Pfizer Inc.
Lucy X. Yang
7000 Portage Road
Kalamazoo, MI 49001
Tel 269.833.9536 Fax 269.833.8897

June 27, 2011

Division of Dockets Management (HFA305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Pfizer Inc. Request for Revision of the Regulatory Review Period Determination for Convenia under 21 CFR § 60.24
FDA Docket No. FDA-2009-E-0087

Dear Sir/Madam:

We refer to the Notice published in the Federal Register, Vol. 76, No. 83, Friday, April 29, 2011, regarding "Determination of Regulatory Review Period for Purposes of Patent Extension; CONVENIA."

Pursuant to 21 CFR § 60.24, this letter requests a revision of the regulatory review period determination for Convenia. The Applicant for this request is Pfizer Inc. The FDA Docket No. is FDA-2009-E-0087. The basis for the revision request is set forth below and in the accompanying papers.

Summary

Applicant submits that the regulatory review period should be the sum of the period from January 21, 2000, to March 13, 2008 (the testing phase) and from March 13, 2008, to April 25, 2008 (the approval phase). The length of the regulatory review period for Convenia is 3019 days. Of this time, 2975 days occurred during the testing phase and 44 days occurred during the approval phase. Revision of the Regulatory Review Period Determination under 21 CFR §60.24 is respectfully requested.

Background

The active ingredient of Convenia is claimed in US Patent No. 6,020,329. Pfizer received FDA approval to market the animal drug Convenia on April 25, 2008. On June 20, 2008, Pfizer submitted an application to the USPTO for extension of patent term under 35 USC §156. On April 29, 2011, the FDA published a Notice regarding its determination of regulatory review period for purposes of patent extension for Convenia in the Federal Register/Vol. 76, No. 83. In the Notice, the FDA determined that the date the investigational new animal drug application (INAD) became effective was July17, 2000, and the date of the new animal drug application (NADA) for Convenia was March 17, 2008. Based on the FDA's determination, the length of the regulatory review period is 2,841 days. Of this time, 2,801 days occurred during the testing phase and 40 days occurred during the approval phase.

Basis for the Request

A regulatory review period consists of two periods of time: a testing phase and an approval phase. At issue for this request is the proper determination of the beginning date of the testing phase and the beginning date of the approval phase for Convenia. Applicant respectfully requests FDA to reconsider:

1) the effective date of the INAD is January 21, 2000 (instead of July 17, 2000), and
2) the initial date of the NADA is March 13, 2008 (instead of March 17, 2008).

1. The Effective Date of the INAD for Convenia

For animal drug products, the testing phase begins when the sponsor obtains the FDA's permission to begin clinical testing of the drug (the date an exemption under §512(j) of the Federal Food, Drug, and Cosmetic Act "the FD&C Act"), or when a major health or environmental effects test became effective, whichever is earlier. *See* 35 USC §156(g)(4)(B). In the FDA's letter dated November 16, 1999 (see Exhibit A), the FDA assigned Pfizer two INAD file numbers, INAD-10612 (dogs) and INAD-10613 (cats). Typically, obtaining an INAD docket marks the beginning of the testing phase.

Applicant has once again reviewed the FDA's letter dated November 16, 1999. If the assignment of the INAD docket numbers was for administrative purposes, Applicant requests the FDA to consider January 21, 2000, as the effective date of the INAD. The FDA accepted the

protocol entitled, "Acute Safety Toleration of UK-287,074 in Dogs" (see Exhibit B) with revisions on January 21, 2000 (see Exhibit C). This acceptance indicated an exemption for the study to begin under §512(j) of the FD&C Act. Convenia was approved on April 25, 2008, based on data that included the results of the Acute Safety Toleration study presented in the protocol, as indicated in the Freedom of Information (FOI) Summary, Target Animal Safety, Drug Tolerance Study (see Exhibit D).

Applicant therefore requests that January 21, 2000, be considered the date of the exemption according to the plain language "whichever is earlier" under §512(j) of the FD&C Act.

2. The initial date of the NADA for Convenia

Under §512 of the FD&C Act, the date on which a sponsor initially submits an application marks the beginning of the approval phase and directly affects the length of the patent term extension. The actual submission date of the NADA was March 13, 2008 (see Exhibit E). The FDA confirmed this submission date in their acknowledgement letter dated March 18, 2008 (see Exhibit F) and in the approval letter dated April 25, 2008 (see Exhibit G). Under the plain language of §512 of the FD&C Act, the initial date of NADA is the date on which a sponsor initially submits an NADA application.

For this reason, Applicant requests initial date for the review of approval phase to be considered as March 13, 2008.

Respectfully submitted,

Lucy X. Yang
Attorney for Applicant
Registration No. 40,259

Pfizer Inc.
7000 Portage Road
Kalamazoo, MI 49001
Tel. (269) 833-9536
Fax (269) 833-8897

EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

INAD 10612 (A0000, Z0001)
INAD 10613 (A0000, Z0001)

NOV 16 1999

Mary E. Harris
Manager, Regulatory Affairs
Pfizer Inc.
Eastern Point Road
P.O. Box 8010
Groton, CT 06340

Dear Ms. Harris:

We refer to your A0000 submissions dated August 5, 1999 regarding development of a long-acting third-generation cephalosporin injectable in dogs (INAD 10612) and cats (INAD 10613). We also reference the Z0001 submissions dated September 7, 1999, which included a proposed agenda for the September 28, 1999 meeting with CVM as well as preliminary product information and basic outlines for clinical field effectiveness protocols. The drug is proposed for the treatment of various susceptible aerobic and anaerobic bacterial infections in the dog and cat.

For administrative purposes we have assigned you file numbers 10612 (dogs) and 10613 (cats) for your Investigational New Animal Drug (INAD) exemptions. Future correspondence regarding these submissions should be identified by their correspondence dates and our file number INAD 10612 (A0000, Z0001) or INAD 10613 (A0000, Z0001). Submit all correspondence regarding this file directly to the Document Control Unit (HFV-199).

We have reviewed the submissions and have the following comments:

(A0000)

1. The information will be retained in the INAD files.

2. Your submissions did not contain a request for a categorical exclusion from the requirement to prepare an environmental assessment (EA). If you feel it is appropriate, please request an exclusion under 21 CFR 25.33(e). Additionally, you must identify the presence, or lack thereof, of extraordinary circumstances as discussed under 21 CFR 25.21.

3. Prior to shipment of a new animal drug for clinical tests in animals, you must submit a "Notice of Claimed Investigational Exemption for a New Animal Drug", in accordance with 21 CFR 511.1(b)(4).

4. Investigational labeling should be affixed to your investigational drug product prior to shipment for studies conducted under 21 CFR 511.1(a) or (b), as appropriate

(Z0001)

1. We have enclosed a copy of our Memo of Conference from the September 28, 1999 meeting.

Should you have any questions or if we can be of further assistance please contact Dr. Linda M. Wilmot, Team Leader, Equine and Antimicrobial Drugs Team. The telephone number is (301) 827-7540.

Sincerely yours,

Elizabeth Luddy

Elizabeth A. Luddy, DVM
Acting Director
Division of Therapeutic Drugs for Non-Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Enclosure (1)

INAD 10612 (Z0001) - dogs
INAD 10613 (Z0001) - cats
3rd Generation Cephalosporin Injectable Soln.

Pfizer Inc.
Eastern Point Road
Mail Stop 8200-40
Groton, CT 06340
(860) 441-1622

MEMO OF CONFERENCE

September 29, 1999

Between: Mary E. Harris
Bill Baker
Ann Jernigan
Larry Ritzhaupt
Robert Six
Representing Pfizer, Inc.

And: Linda Wilmot, HFV-114
Marilyn Martinez, HFV-130
John Baker, HFV-110
Lisa Kinney, HFV-114
Tania Woerner, HFV-114
Liz Reese, HFV-114
Cacia Masser, HFV-114
Dennis Bensley, HFV-143
Raafat Fahmy, HFV-142
Representing CVM

Drs. Baker, Jernigan, Ritzhaupt, and Six, and Ms. Harris met with CVM on September 28, 1999 to discuss INAD 10612 (Z0001) and INAD 10613 (Z0001) for the development of a third-generation cephalosporin injectable solution with an extended half-life for use in dogs and cats, respectively. The following salient points were discussed:

1. The firm provided some background information on the product:

   It is a stereoisomer (single isomer, versus racemic mixture). The proposed final form is a lyophilized powder with preservative (as yet unknown which preservative will be chosen). The firm feels that they have demonstrated that the pharmacokinetics of IV versus subcutaneous administration are comparable in terms of terminal half-life. The drug is highly protein-bound (>99%). Pk_a is unknown. The MIC_{90} for the pathogens of interest ranges to 1.0 µg/ml with the exception of Clostridium spp, for which this data was not collected, but the MIC_{50} ranged to 2.0 µg/ml. In general, the anaerobes and gram-negative organisms demonstrated higher MIC values than did aerobes. The drug half-life is just under 5 days.

The firm has performed a wound model study with this product, wherein the test product compared favorably with a saline negative control and to a cefadroxil positive control for aerobic organisms. It is the opinion of the firm that the test drug appeared somewhat less efficacious against anaerobic bacterial infections because of the dose chosen and the relatively high MIC values for anaerobic organisms. The firm proposes that this study provides evidence that the drug is releasing from protein and is present in an active form (versus unavailable to tissues or inactivated by plasma protein binding). The firm feels that this study also provides preliminary evidence of sustained efficacy.

2. Regarding the proposed pharmacokinetic and bioavailability study design, CVM indicated interest in establishing the linearity of plasma profiles in the 4-12 mg/kg range given subcutaneously (proposed dosage). We discussed that pharmacokinetic and MIC data are helpful in providing a dosage rationale. The firm suggested that they would revise study design as necessary to support the desired professional flexible label.

   CVM discussed the possibility of evaluating plasma samples to determine drug levels in cases of therapeutic failures.

3. Superficial pyoderma protocol outline:

   Superficial pyoderma is a problematic claim to support. Issues of general concern regarding this claim are:

   Duration of therapy required. The recommended duration of a 1X, 3X, 5X target animal margin of safety study is three times the intended duration of use. Superficial pyoderma, according to standard veterinary texts, should be treated with antimicrobials for several weeks.[1] The required target animal safety study duration would be extended accordingly.

   The complexity of the etiology and its relationship to uniform case selection. Superficial pyoderma is a fairly narrowly defined entity, but determining for the label which aspects of the disease (generalized versus localized, primary versus secondary, etc.) have been experimentally addressed is difficult. After deciding which label claims are attainable and appropriate, it is recommended that the firm consider performing the field studies with investigators specializing in veterinary dermatology.

   Describing/evaluating for clinical relapse such that the label can address the relapse issue. Considering the long half-life of this drug, the interval from treatment to plasma drug levels below MIC could be inordinately long .

[1] Ettinger SJ and Feldman EC, Eds., Textbook of Veterinary Internal Medicine, 5th Ed, WB Saunders, 2000, pp. 46-7.

Positive controls. The only drug with a label claim for pyoderma is cefadroxil. Positive control studies are held to a statistical standard of "not worse than" the positive control, which can be more statistically exacting than negative control standards, requiring a larger data set. A negative control is less complex, but presents ethical concerns. We discussed a possible "rescue" design, wherein the negative controls would be considered treatment failures fairly early on, removed from the study, and administered an appropriate antibiotic.

Offering 3 dosage regimens (4, 8, and 12 mg/kg) with a difficult-to-clinically-define disease entity would require high numbers of dogs.

The firm clarified that the intended label claim would be for a 28-day duration of use; the 35-day study listed on page 20 would not be listed on the label.

4. The number of cases is listed as 20-40 in these protocol outlines; generally we recommend ≥ 75 cases per treatment group. The firm stated that they intend to have at least 40 evaluable cases per treatment group, and will include power calculations when they submit the protocols.

5. Skin and Soft Tissue protocol outline:

   Considering the protracted half-life of this drug, clinical resolution evaluation after drug washout is an issue pertinent to this protocol.

   For minor to moderate wounds/lacerations/abscesses, a 28-day duration of treatment period would appear excessive. If a wound were not healed at day 21 but by day 28 had resolved, we would not consider that case a success. Consider that there is a high rate of spontaneous resolution of these cases with time. The firm may wish to further define this category, and narrow the claim to, for instance, mild to moderate wounds and abscesses, which would dictate shortening the study duration.

6. Urinary Tract Infection protocol outline:

   Cefadroxil is approved for UTI in dogs but not cats. It would be an appropriate positive control in dogs with UTI but not in cats with UTI.

   CVM asked the sponsor to address the problem of obtaining post-treatment urine cultures that do not contain residue antimicrobial levels that may confound the ability to interpret the results.

7. Periodontal Infection protocol outline:

   The proposed endpoint is reduction in gingival index, which is a measure of gingival inflammation. This would seem inadequate, and the firm stated that gingival index is one of several endpoints - they will forward additional information in the protocol submission.

The firm intends to incorporate veterinary dental specialists as investigators for this study.

The duration of treatment will be determined by the endpoint chosen.

8. Feline Upper Respiratory Infection protocol outline:

   Study design is key to determination of appropriate cases for clinical evaluation. CVM expressed concern regarding the ambiguities inherent in feline upper respiratory infections - primary versus secondary (viral, traumatic, neoplastic, foreign body, etc.), acute versus chronic (with chronic disease being much more invasive of the cartilage and bone, therefore the approach to treatment is different), determination of pathogens (even with culture they can be challenging to identify, as secondary pathogens are often normal flora; in addition, culture acquisition can be technically problematic), etc.

   The firm responded that they would probably target acute cases of bacterial upper respiratory infection secondary to viral infections. Culture may be appropriate, depending upon the actual label claim desired. The firm will reconsider whether to narrow the label claim or expand the inclusion criteria/data sets, as well as define criteria for success (clinical? negative culture?).

   The firm has proposed a positive control such as cefadroxil. The paucity/absence of products carrying a label claim for feline upper respiratory infections could be a challenge. For ethical reasons, the firm could consider a negative control study with a rescue provision.

9. The firm inquired whether a 10X drug tolerance study would be required to support product safety, as the toxicities associated with cephalosporins as a class are well-characterized. We cannot respond definitively without the submission of written scientific justification accompanied by supportive literature. One CVM concern regards a bleeding tendency demonstrated by a structurally-based subset of this drug class - the firm should consider incorporating clotting profiles into the safety studies. It is possible that when the 5X dose level is administered repeatedly in the 1X, 3X, 5X study the C_{max} may meet or exceed that of a 10X dose through accumulation, and the 5X blood levels may satisfy the 10X requirement.

10. Page 31 was modified - the endpoints of the "Toleration Study Design: Dosing for 3 Months" now include "Injection site assessments after the first FOUR treatments."

11. The current formulation is a non-GMP lyophile reconstituted with sterile water. The final market formulation will be a GMP lyophile with *preservative(s)* reconstituted with sterile water. CVM gave the firm an option to submit a request for waiver of a bioequivalency study by characterizing the current lyophile (purity, etc.), and submitting that information, along with careful descriptions of the final market

formulation, to CVM prior to starting studies. In addition, we discussed that performing the safety studies with the current formulation, though not optimal, may be acceptable if the chosen preservative is well characterized. In this case the firm could incorporate into the clinical trial forms an assessment of the injection site by the investigator/owner. In establishing bioequivalence, the analysis would not necessarily be in strict accordance with the 1996 CVM Bioequivalence Guidance document. Statistical evaluation would take into account the therapeutic index, etc. in establishing the appropriate statistical model.

12. The firm stated that the shelf-life after reconstitution is projected to be 30 days (unkown whether refrigeration required); unreconstituted product is projected to last 2 years. Though the product is fairly resistant in current form to bacterial contamination, the firm is adding the preservative in order to reduce fungal growth. The product will likely be supplied as a 10 ml vial, with a cephalosporin concentration of 80 mg/ml.

The firm resolved to internally discuss the information gathered today in order to develop study protocols supporting U.S. approval of INADs 10612 and 10613. The firm agreed to submit the protocols to CVM for review prior to implementing the studies.

Lisa A.H. Kinney, DVM
Veterinary Medical Officer
HFV-114

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 4414100

Central Research

EXHIBIT B

November 10, 1999

Dr. Linda Wilmot, HFV-114
Division of Therapeutic Drugs for Non-Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: INAD I0-612 UK-287,074 (Cephalosporin) Injectable for Dogs
Drug Tolerance Protocol Review Request

Dear Dr. Wilmot:

We request review of the enclosed protocol 99-1990-01 entitled 'Acute Safety Toleration." As we discussed in our pre-development meeting on September 28, 1999, this compound is a third generation cephalosporin, a class of drugs for which toxicity is well characterized. At our meeting, we agreed that blood coagulation tests are appropriate for this class of drug, and that animals need not be sacrificed for necropsy at study end unless significant clinical signs related to treatment are observed. We have incorporated these procedures in the enclosed site-specific protocol.

We wish to point out that, although normal Pfizer procedure is to gain agency concurrence on a master protocol, the enclosed protocol on which we seek your comments is specific to Pfizer's Central Research facility here in Groton. We intend to follow standard Pfizer Drug Safety Evaluation procedures while conforming to the recommendations in CVM's Target Animal Safety Guideline as discussed at our meeting. We have appended several relevant documents to provide you more detail than is normally incorporated in Pfizer's acute safety toleration test (for human drug testing).

Thank you for your consideration. If any questions arise during your review, please call me at (860) 715-2562.

Sincerely,

Robert Chesebrough
Manager, Regulatory Affairs

Department of DRUG SAFETY EVALUATION
GROTON, CONNECTICUT

PROTOCOL	STUDY DIRECTOR Cynthia J. Davenport, Ph.D.

Compound No.: UK-287,074 **Study No.:** 99-1990-01 **Date:** January, 2000	**Species:** Mongrel Dog **ACUP#:** 0636	**Study Type:** Acute Safety Toleration

Animals - **Breed/Strain:** Mongrel **Room No:**
Age/Weight: 5-12 months
Source: Butler Farms
Total No.: **Males** 6 **Females** 6
RODENTS - Starting Animal No.: **Males** NA **Females** NA

Compound - **Biological Activity:** Cephalosporin antibiotic (Animal Health)
Hazards: Personnel with known allergies to penicillin or cephalosporins should not handle UK-287,074.

Standard Protocol: NA
Deviation(s) from Standard Protocol: NA

Purpose of Study: To assess the acute toxic effects of a single subcutaneous dose of UK-287,074 in dogs.

Dose Levels: **Number of Animals/Dose Group**

	Group 1 Saline Control 2.25 ml/kg	Group 2 UK-287,074 180 mg/kg			
Males	3	3			
Females	3	3			
Total	6	6			

Dose Level/Route Rationale: The dose chosen is 10X the maximum anticipated clinical dose (18 mg/kg). The drug is to delivered subcutaneously in veterinary clinical patients.

Regimen - **Route:** Subcutaneous **~~Gavage/In Diet/~~Injection Site:** Scapular region
Vehicle: Saline (0.9% Sodium chloride) Dose volume = 2.25 ml/kg
Frequency: Single dose

Start of Study: January, 2000
Duration of Treatment: Single dose, 10 day observation period
End of Study: February, 2000

1892 (Rev 6/98)

PROTOCOL

Compound No.: UK-287,074 | **Species:** Mongrel Dog

Study No.: 99-1990-01 | **Date:** January, 2000

Clinical Pathology Test Procedures:

☐ Not Requested

☒ Requested - See attached Clinical Pathology Request Form No. 6220 and Appendix A.

Pathology:

☐ Not Requested ☒ Other (See Instructions Page 3 and Appendix A)

☐ Standard Tissues

Pharmacokinetics/Absorption Tests:

☐ Not Requested

☒ Requested – See Appendix A

Animal Model: Selection / Identification: The mongrel dog is selected for its similarity to veterinary clinical patients. Identification is according to Standard Procedure AR-78-05 and TOX-76-10 (attached).

Dates	Day	Hematology	Clin. Chem.	Urine	Necropsy	Other
TBD	Pre	NA	NA	6M + 6F	NA	Fecal exam (6M + 6F)
TBD	Pre	6M + 6F	6M + 6F	NA	NA	NA
TBD	1	NA	NA	NA	NA	Dosing (6 M + 6F)
TBD	10	NA	NA	6M + 6F	NA	Fecal exam (6M +6F)
TBD	11	6M + 6F	6M + 6F	NA	6M + 6F (tentative)*	NA

*See Special Instructions, page 3.

Toxicology:

Appearance / Clinical Signs: Once daily pre-study and on the day of dosing at least pre-dose, immediately post-dose, 2, 4 and ~4-8 hours post-dose.

Body Weight: At least once pre-study and on days 1, 4, 7 and 11.

Food Consumption: Food assessment daily beginning approximately 1 week prior to day 1.

Other: Physical Examinations and Vital Signs – Once pre-study and at the end of the study (day 11).

Compound No.: UK-287,074	**Species:** Mongrel Dog
Study No.: 99-1990-01	**Date:** January, 2000

Diet: All dogs will receive a standard diet of dry food (Certified Canine Diet 5007, PMI Feeds, Inc.) once daily. Drinking water will be supplied *ad libitum* through an automatic watering system with founts in each cage. Water is obtained from a municipal water system subject to the regulations of the Environmental Protection Agency and is further purified by a reverse osmosis system prior to reaching the animal room. To the best of our knowledge, there are no potential contaminants present in the diet or drinking water that would alter the pharmacologic or toxicologic profile of the test substance or likely to be present in sufficient quantities to influence the results or this investigation.

Statistical Methods: Treated group means will be compared to control means using two-tailed Dunnett's or the Cochran-Cox t-test depending on results of a preliminary Bartlett's test for variance homogeneity.

Special Instructions:

Necropsy – If significant clinical signs related to treatment are observed in any animal, then on day 11 (at the discretion of the Study Director) all animals will be euthanatized, a necropsy will be performed and tissues will be collected as described in Appendix A. If no significant clinical signs are observed, dogs will be transferred to the Exploratory dog colony.

Record-keeping, randomization, housing, husbandry and drug-carrier mixing and control will follow documented standard laboratory procedures.

Department of DRUG SAFETY EVALUATION
GROTON, CONNECTICUT

Compound No.: UK-287,074

Species: Mongrel Dog

Date: January, 2000

Study No.: 99-1990-01

RESPONSIBLE INVESTIGATORS:

Toxicology:	Cynthia J. Davenport, Ph.D.	**Pathology:**	To Be Determined
	To Be Determined		
Issued By:		**Approved By:**	

REVIEWED BY (initials):

Dr. Ronfeld _____ Dr. Holmes _____ Dr. Levinsky _____

Dr. Kinkler _____ Dr. Ochoa _____ Dr. Kluwe _____

Approved: _____ Date: _____
Senior Technical Advisor

Approved: _____ Date: _____
Pathologist

Approved: _____ Date: _____
Study Director

CIRCULATION LIST

Dr. Cronin (Ag.)
Ms. Duzant (WJD/CLH)
Mr. Gerber
Mr. Kadyszewski / Ms. Todd
Dr. Kinkler
Dr. Levinsky
Mr. McLarnin
Dr. Mehta (Med.)
Dr. Paulus
Discovery Research (Med.) /
ECMT Chairman: Dr. D. D. Mann

Dr. Ronfeld
Ms. Rosen
File
Original - Protocol File
Metabolism: Dr. E.L. Nimz
Study Technician: M. Knickerbocker
Toxicologist: NA
Pathologist: NA
Study Director: Dr. C.J. Davenport
Other: Dr. D. K. Blackwell, Dr. R. H. Six

QUALITY ASSURANCE UNIT
INSPECTION / AUDIT

☒ Required
☐ Not Required

Appendix A

EXPERIMENTAL PROCEDURE

1. DATES OF STUDY AND CALENDAR OF EVENTS

Events/Observations	Day of study (time)[a]	Groups
Clinical signs	Once pre-study At least twice daily during study On the day of dosing at least pre-dose, ipd[b], 2, 4 and ~4-8 hpd[b]	All
Body weight	Once pre-study Days 1, 4, 7 and 11	All
Food assessment	Daily starting one week prior to day 1 Days 1-11	All
Urinalysis and fecal examination	Once pre-study Day 10	All
Hematology and serum chemistry	Once pre-study Day 11	All
Physical examination and vital signs	Once pre-study Day 11	All
Necropsy	Day 11 (tentative)[c]	All

[a] Unless otherwise noted, "day" refers to the number of days from the initial day of dosing, not study calendar days.
[b] ipd = immediate post-dose; hpd = hours post-dose
[c] Detailed in necropsy section below.

2. MATERIALS

Compound

Compound number:	UK-287,074
Lot number:	To be determined
Active moiety:	To be determined
Purity/composition:	To be determined
Storage conditions:	To be determined
Expiration date:	To be determined

Vehicle

A buffered vehicle (commercial prototype; pH = 7) will be used in the preparation of the subcutaneous dosing formulation.

Stability and Verification of the Formulated Compound

Representative samples of the UK-287,074 formulation used for dosing will be obtained and submitted for assay to verify potency. Information from independent studies performed to determine stability and storage conditions of the dosing formulation, as well as filter and syringe compatibility with the dosing formulation will be made available.

Animals

Mongrel dogs obtained from Butler Farms will be used in this study. A total of 8 males and 8 females will be acclimatized to our laboratory prior to dosing. From these, 6 males and 6 females will be randomly assigned according to body weight using a computer program to 2 groups of 3 per sex per group. The dogs will be approximately 5 to 12 months old.

Each dog will be identified by an ear tattoo and an identification number on a steel plate on the dog's collar. Each cage will be labeled with compound number or control, prerandomization number, study animal number, cage number, ACUP number, sex, species, route of administration and dose level on a color coded card. For convenience, sequential numbers will be assigned to the dogs at randomization and will be used in this study to identify individual animals.

The dog is our standard non-rodent test species and is generally accepted as a test species in toxicity studies. Mongrel dogs were selected for use in this study because of their similarity to veterinary clinical patients.

Housing conditions

The dogs will be housed individually in four by six foot runs. Room design specifications for environmental conditions are single pass air supply with a minimum of 12 air changes per hour with air filtered through 80-85% efficiency pre-filters, relative humidity of 45 ± 10%, temperature of 70 ± 5°F and a 12 hour light/dark cycle.

A standard diet of dry food (Certified Canine Diet 5007, PMI Feeds, Inc.) will be provided once daily and municipal drinking water, further purified by reverse osmosis, will be provided *ad libitum*. To the best of our knowledge, there are no contaminants in the diet or water that could be expected to interfere with the outcome of this study.

3. METHODS

Preparation and administration of compound/vehicle

Prior to dosing, a 80 mg/ml buffered solution of UK-287,074 will be prepared. The UK-287,074 dosing solution will be administered by subcutaneous injection using an appropriately sized syringe (3 ml syringe for volumes between 1 and 3 ml; 5 ml syringe for volumes between 3 and 5 ml; 10 ml syringe for volumes between 5 and 10 ml; 20 ml syringe for volumes between 10 and 20 ml) fitted with a 22 gauge needle. A new syringe and needle will be used for each animal. Injections will be accomplished by lifting the loose skin on the lower portion of the neck (interscapular region) and inserting the tip of the needle into the subcutaneous space where the solution will be injected. Although the routine maximum subcutaneous injection volume for multiple dose studies in dogs is 1 ml/kg/site, administration of the prescribed dosing volume (2.25 ml/kg) in this single dose study will be performed using two injection sites. Approximately one-half of the required dose will be delivered into the subcutaneous tissues in the left scapular region and the remainder of the dose will be injected into the right scapular region. Control animals will be dosed with saline in the same manner.

4. OBSERVATIONS AND MEASUREMENTS

Clinical observations/measurements

Mortality/Appearance/Behavior

All dogs will be observed (at least once daily pre-study and twice daily after dosing) in their cages for signs of toxicity and for any changes in appearance or behavior. On the day of dosing, all animals will be observed at least pre- and immediately post-dose, 2, 4 and approximately 4-8 hours post-dose.

Body weight

Body weights will be determined once prior to the initiation of dosing, on the day of dosing (day 1) and on days 4, 7 and 11 during the study period.

Food assessment

Daily food consumption will be visually estimated beginning approximately 1 week prior to dosing and on each study day thereafter as either <25%, 25-50%, 51-75%, 76-99% or 100%.

Physical examinations/vital signs

Physical examinations will be performed on all dogs once prior to dosing and again at the end of the study (day 11). Vital signs including respiratory rate, heart rate, and rectal temperature, along with an assessment of the general physical condition of the animal, will be recorded at the time of each physical examination. Heart rate will be determined by thoracic auscultation.

Clinical laboratory measurements

Sample collection

Blood samples for hematology and serum chemistry determinations will be collected by jugular venipuncture from all dogs (fasted) once prior to the day of dosing and on day 11. Urine and fecal samples will be collected from all animals within approximately 24 hours of sample collection for clinical pathology. Urine will be collected by free catch and at room temperature over an approximate 5-6 hour period. The following measurements will be made:

Hematology

The following parameters will be measured on the Technicon H*1 unless otherwise indicated.

red blood cell count (RBC, $x10^6/mm^3$)
hemoglobin concentration (HGB, g/dl)
hematocrit (HCT, %)
platelet count (PLT, $x10^3/mm^3$)
mean corpuscular volume (MCV, fl)
mean corpuscular hemoglobin (MCH, pg)
mean corpuscular hemoglobin concentration (MCHC, %)
white blood cell count (WBC, $x10^3/mm^3$)
white blood cell differential count (WBC Differential, % and absolute)

neutrophils (N, %)	(NCT, $/mm^3$)
lymphocytes (L, %)	(LCT, $/mm^3$)
monocytes (MO, %)	(MOCT, $/mm^3$)
eosinophils (EO, %)	(EOCT, $/mm^3$)
basophils (B, %)	(BCT, $/mm^3$)
large unstained cells (LUC, %)	(LUCT, $/mm^3$)

Reticulocyte counts (RET, %) will be determined on the Sysmex R3000.

The following coagulation tests will be conducted using the ACL 3000+:

prothrombin time (PT, sec)
activated partial thromboplastin time (APTT, sec)

Serum chemistry

The following assays will be conducted on either the Hitachi or COBAS clinical chemistry analyzer:

alanine aminotransferase (ALT, U/L)
alkaline phosphatase (ALP, U/L)
amylase (AMYL, U/L)
total bilirubin (TB, mg/dL)
total protein (TP, g/dL)
albumin (ALBM, g/dL)
glucose (GLUC, mg/dL)
potassium (K, meq/L)
creatinine (CREA, mg/dL)
sodium (NA, meq/L)
chloride (CL, meq/L)
aspartate aminotransferase (AST, U/L)
γ-glutamyl transferase (GGT, U/L)
lactate dehydrogenase (LDH, U/L)
bile acids (BILA, µM/L)
phosphorus (P, mg/dL)
cholesterol (CHOL, mg/dL)
blood urea nitrogen (BUN, mg/dL)
creatine phosphokinase (CK, U/L)
calcium (CA, mg/dL)

Globulin (GLOB, g/dL) will be calculated.

Urinalysis/Fecal Examination

The following measurements will be conducted on the CLINITEK 200 unless otherwise indicated:

volume (VOL, ml, manual)
specific gravity (SPGR, refrac.)
pH (5 to 9)
protein (PRO, neg to 4+)
blood (BLO, neg to 3+)
glucose (GLU, neg to 4+)
urobilinogen (URO, neg to 4+)
bilirubin (BIL, neg to 3+)
ketones (KET, neg to 4+)
color (COLR, visual assessment)

Microscopic examination of sediment will be executed if urine is abnormal in color and/or blood (3+) was observed.

Microscopic analysis of urine sediment will include the following rated on a scale of negative to 4+ and TNTC (too numerous to count):

casts (CAST, /lpf)
red blood cells (RBC, /hpf)
calcium oxalate crystals (CAOX, /lpf)
triple phosphates (TRPH, /lpf)
other crystals (OTHR, /lpf)
white blood cells (WBC, /hpf)
epithelia (EPTH, /lpf)
amorphous phosphates (AMPH, /lpf)
amorphous urates (AMUR, /lpf)

Fecal samples will be examined for the following parameters:

Consistency
blood or other signs of hemorrhage (visible)
parasites

Plasma drug concentrations

Blood samples (approximately 3 ml) will be collected via jugular venipuncture from drug-treated and control animals at approximately 1.5, 24, 48, 96 and 240 hours post-dose to determine plasma concentrations of UK-287,074. Collected blood samples will be processed and the separated plasma stored frozen until analysis.

Postmortem observations

Necropsy

If significant clinical signs related to treatment are observed in any animal, then on day 11 (at the discretion of the Study Director) all animals in both treatment groups will be euthanatized and necropsied. All dogs will be fasted overnight prior to necropsy, anesthetized by an intravenous injection of pentobarbital sodium and exsanguinated on day 11. Following an external examination, each carcass will be opened and all internal organs removed for visual examination. Samples of the organs listed below plus any macroscopic lesions will be collected and placed in fixative.

kidneys	ovaries
urinary bladder	uterus
aorta	cervix
liver (left and right lateral lobes)	trachea
thymus	lung (multiple lobes)
spleen	heart
mesenteric lymph node	peripheral nerve
esophagus	brain (cerebrum, cerebellum and pons)
stomach	spinal cord (cervical)
duodenum	eyes
jejunum	skin and adnexa
ileum	mammary gland
cecum	bone (sternum, including marrow)
colon	pituitary gland
gall bladder	salivary gland
pancreas	adrenal glands
thyroid gland	parathyroid
testes (left and right)	epididymides
prostate	injection site
skeletal muscle	

Organ weights

Body weights and the weights of the kidneys (combined), liver, testes (combined), adrenals (combined), pituitary, ovaries (combined), brain and heart will be recorded and organ to body weight ratios calculated.

Tissue processing and microscopic examination

Eyes will be fixed in 3% glutaraldehyde in Sorenson's buffer. All other organs/tissues and macroscopic lesions will be fixed in 10% neutral buffered formalin. Following fixation, tissues will be trimmed, dehydrated, embedded in paraffin, sectioned, mounted on glass slides and stained with hematoxylin and eosin.

Microscopic examination

The processed tissues listed above and macroscopic lesions of all dogs will be examined by light microscopy. Following completion of the tissue evaluation by the study pathologist, a second pathologist will perform a peer evaluation.

5. DATA EVALUATION

The following parameters will be analyzed statistically: clinical pathology, body weights, vital signs and organ weights. Statistical analyses will be executed separately for males and females as follows: For each collection period, each treated group mean will be compared with the control group mean. Dunnett's[1,2] multiple comparison procedure will be used if a preliminary Bartlett's[3] test for variance homogeneity is not significant at the α=0.05 level. If there is significant variance heterogeneity, the Cochran-Cox modified t-test[4] will be used for comparison between treated and control group means. Statistical significance of the comparisons will be indicated at both the α=0.05 and 0.01 levels. Tests will be two-tailed.

For the purpose of data interpretation, statistical significance will not be considered to automatically imply toxicological significance. Conversely, the absence of a statistically significant comparison is not considered to imply the lack of a biologically important effect.

1. Dunnett CW. A Multiple Comparison Procedure for Several Treatments with a Control. Journal American Statistics Association 1955;50:1096-121.

2. Dunnett CW. New Tables for Multiple Comparisons with a Control. Biometrics 1964;20:402-92.

3. Sokal R, Rohlf FJ. Biometry. W.H. Freeman and Co., San Francisco, 1969.

4. Cochran WG, Cox GM. Experimental Designs. John Wiley, New York, 1959.

Department of DRUG SAFETY EVALUATION

Clinical Pathology

LABORATORY TEST PROCEDURES

COMPOUND NO.	STUDY NO.	SPECIES	TECHNICIAN
UK-287,074	99-1990-01	CANINE	

CLINICAL CHEMISTRY:

Core Tests (Individual tests may be selected by circling them)
X Glucose, BUN, creatinine, total protein, albumin, calculated globulin, calcium, sodium, potassium, chloride, total cholesterol, ALT, AST, γGT, total bile acids (fasted) and total bilirubin (direct bilirubin will be run if total >1.0 mg/dl), alkaline phosphatase.

Other Tests

Electrolytes
__Mg
X P
__Total CO_2

Hepatic
__SDH

Pancreatic
X Amylase
__Lipase

Thyroid
__T_3
__T_4

Endocrine
__Testosterone
__Progesterone
__Cortisol
__Insulin

Lipids
__Triglycerides
__HDL

Miscellaneous
X CK
X LDH
__Iron/TIBC
__Lactic acid (grey top tube)

HEMATOLOGY:

Core Tests (Individual tests may be selected by circling them)
X CBC (WBC, RBC, HCT, HGB, MCV, MCH, MCHC, PLT & WBC differential), prothrombin time, activated partial thromboplastin time & reticulocyte count.

Other Tests

Coagulation
__Fibrinogen
__FSP (special tube)
__ATIII

Miscellaneous
__Erythrocyte Osmotic Fragility

URINALYSIS:

X Routine Urinalysis
X Urinary sediment
__Fecal occult blood

Urinary electrolytes
__Na __Ca
__K __Mg
__Cl __P

ADDITIONAL TESTS/INSTRUCTIONS

Fecal flotation for parasites

ISSUED BY: _____ Date _____

APPROVED BY:
Toxicology _____ Date _____
Clinical Pathology _____ Date _____

GROTON, CT

STANDARD PROCEDURE

DRUG SAFETY EVALUATION

Section:	CMBS
No.:	CM-78-05
Effective:	June 1, 1999
Page:	1 of 3
Approved:	

Supersedes: AR-78-05; October 15, 1997

Subject: CMBS ANIMAL IDENTIFICATION SYSTEM (BUILDING 274)

General:

The CMBS department issues individual identification numbers for all species, except rats, mice, and hamsters. The CMBS department does not issue numbers for any rabbits ordered for the Reproductive Toxicology department. Appropriate information is described in Reprotox 91-06. Identification numbers are listed on the Request for Animals Form 6450-11G, and are derived from a sequential numbering system kept for each species. Depending on investigator needs, numbers may be issued at the time the Request for Animals Form is submitted, upon arrival to the facility, or at any time in between. The CMBS animal numbering system indicates the following:

- species
- year
- sex
- unique number for that animal

e.g., 03-99-30001 or 03-99-00001

-03- indicates species is beagle
-99- indicates the year is 1999
-3- indicates animal is male (first of last 5 digits)
-0- indicates animal is female (first of last 5 digits)
-0001- unique animal number (last 4 digits)

Species designation for various animals currently being used is as follows:

02	Monkey
03	Beagle
05	Rabbit
08	Cat
12	Guinea Pig
24	Purpose Bred Mongrel

INDIVIDUAL RECORD FILES:

The CMBS department issues individual record cards for cats, dogs, and primates. Individual record cards are not issued for rats, mice, hamsters, guinea pigs, or rabbits. Individual record cards for cats, dogs, and primates are maintained in the animal's individual file in the CMBS Supervisors office until the animal is assigned to a study. CMBS will stamp the individual record card with the ACUP number and the date assigned to study. At that time, the file is transferred to the Toxicology Technician responsible for the study. Animals designated as surplus following pre-selection examinations will be returned to CMBS, and any significant findings will be documented on the individual record card. Both the Toxicology Technician and the Study Director will initial the individual record card. If placed on study, the individual file is returned to the CMBS office prior to the end of the first week of dosing. The individual files will be kept in the CMBS Supervisor's office.

Section:	CMBS
No.:	CM-78-05
Effective:	June 1, 1999
Page:	2 of 3
Approved:	5/7/99

Supersedes: AR-78-05; October 15, 1997

Subject: CMBS ANIMAL IDENTIFICATION SYSTEM (BUILDING 274)

An entry indicating the study number, test article, dose level(s) received (mg/kg), and the final disposition of the animal, will be included on the individual record card. Both the Toxicology Technician and the Study Director will initial the individual record card. Animals that have been euthanized, or died, will have their individual record cards processed, and the file will be sent to the CMBS main office complex in Bldg. 118C for filing. Individual record cards will be returned to the central files in Bldg. 274 when requested.

TATTOOING / CAGE IDENTIFICATION

Cats:
Cats are tattooed by the vendor on the inside of their ear with an USDA identification number. This number, in addition to the animal's identification number assigned by CMBS, is recorded on the animal's individual record card. Cat cages are identified with a card that includes the cat's 5-digit identification number assigned by CMBS and vendor USDA tattoo number.

Dogs:
Dogs are tattooed by the vendor on the inside of their ear with an USDA identification number. This number, in addition to the animal's identification number assigned by CMBS, is recorded on the animal's individual record card. The dog's CMBS 5-digit identification number is also imprinted on a steel plate attached to a collar. Single housed dogs generally will wear a collar. Dog runs/cages are identified with a card that includes the dog's CMBS 5-digit animal number and vendor USDA tattoo number. Dogs assigned to a study will have new cards generated that include appropriate information as described in Toxicology Standard Procedures TOX-76-10.

Primates:
Primates are tattooed by the vendor with an USDA identifying number on their arms or legs, but usually not on the chest. Within a few days of arrival the last three digits of the CMBS 5-digit number is tattooed on the animal's chest. The animal's cage is marked with the individual's CMBS 5-digit number using a water resistant pen, or a cage card is generated and placed in the cage card holder. Primates assigned to a study will have cage cards generated that include appropriate information as described in Toxicology Standard Procedure TOX-76-10. This card is affixed on the caging (or assoc. equipment) to clearly designate the animal.

Rabbits:
All rabbit cages are labeled with cage cards including appropriate information as described in Toxicology Standard Procedure Tox-76-10 or Reprotox 91-06. All rabbits arrive with vendor numbered ear tags. Within a few days of arrival, rabbits ordered for Toxicology studies will have one ear tattooed with the CMBS 5-digit number. This procedure is performed by a CMBS Technician. Rabbits ordered for Reproductive Toxicology studies are not tattooed, but are retagged by the Reprotox Technician as described in Reprotox 91-06.

Rats/Mice
The vendor does not individually identify these animals. Identifying numbers, tattooing, and cage labeling is performed as per Toxicology Standard Procedure TOX-76-10 or Reprotox 91-06.

GROTON, CT

STANDARD PROCEDURE

DRUG SAFETY EVALUATION

Section:	CMBS
No.:	CM-78-05
Effective:	June 1, 1999
Page:	3 of 3
Approved:	

Supersedes: AR-78-05; October 15, 1997

Subject: CMBS ANIMAL IDENTIFICATION SYSTEM (BUILDING 274)

Guinea Pigs/Hamsters

These animals are not individually identified by the vendor, but may be issued unique animal numbers by CMBS. They are not tattooed.

GROTON, CT

STANDARD PROCEDURE

DRUG SAFETY EVALUATION

Section:	TOXICOLOGY
No.:	TOX-76-10
Effective:	June 1, 1999
Page:	1 of 3
Approved:	Sarah A. Griffin 5/20/99

Supersedes: TOX-76-10 Dated April 3, 1995

Subject: RANDOMIZATION, IDENTIFICATION OF ANIMALS AND CAGES, AND CLEANING OF RACKS AND CAGES

RANDOMIZATION

RATS AND MICE

A computer randomization program will be used to assign animals to dose groups by body weight (optional for Exploratory studies). A record of the computer randomization will be signed and dated by the Study Director or designate and become part of the study notebook. Animals will be housed in cages in the following sequence: starting in the top left hand corner of the first rack and always proceeding from the top to the bottom of each column (e.g. control, low, intermediate and high dose males followed by females in the same dose group order). Males and females will be housed on separate sides of a rack or on a different rack(s) when possible (optional for Exploratory studies).

For Acute studies, mice and rats are selected at random and sequentially assigned to dose groups without conscious bias by the Toxicology Technician prior to treatment initiation. A record of the one-one-computer randomization will be signed and dated by the Study Director or designate and become part of the study notebook. Animals can be housed individually in hanging wire cages or group housed by sex and dose group in the appropriate polycarbonate cages.

DOGS, MONKEYS AND RABBITS

A computer randomization program will be used to assign animals to dose groups by body weight (optional for Exploratory studies). A record of the computer randomization will be signed and dated by the Study Director or designate and become part of the study notebook. For dogs, when birth records are available, an attempt will be made to assign animals from the same litter to different dose groups (optional for Exploratory studies). Animals will be housed individually in stainless steel wire suspended cages (monkeys and rabbits) or in runs (dogs).

RANDOMIZATION (ONCOGENICITY STUDIES)

RATS AND MICE

A computer randomization program will be used to assign animals to dose groups by body weight. A second computer randomization is then performed to assign rodents to random cage positions within the room. A record of each computer randomization (by body weight and cage position) will be signed and dated by the Study Director or designate and become part of the study notebook. Male and female rats are housed in different rooms. Male and female mice are housed in the same room, but in different racks on separate sides of the room (when possible). Animals will be housed in the rack in numerical cage order starting in the top left hand corner and proceeding from top to bottom of each column.

GROTON, CT

STANDARD PROCEDURE

DRUG SAFETY EVALUATION

Section:	TOXICOLOGY
No.:	TOX-76-10
Effective:	June 1, 1999
Page:	2 of 3
Approved:	Sarah A. Griffin 5/20/99
	Tammy Nyden 5/20/99
	Stanley W. Stadnicki 5-20-99

Supersedes: TOX-76-10 Dated April 3, 1995

Subject: RANDOMIZATION, IDENTIFICATION OF ANIMALS AND CAGES, AND CLEANING OF RACKS AND CAGES

IDENTIFICATION OF ANIMALS AND CAGES

RATS AND MICE

Prior to randomization, cages housing animals will be identified with sequentially numbered cards beginning with the males, and followed by the females (e.g. pre-study animal numbers 1-43, males; 44-86, females).

For Acute studies, prior to randomization, cages or shoe boxes housing animals will be identified with a cage card containing the following information: study number, sex, responsible technician, responsible Study Director, and ACUP number.

At the time of randomization, each study animal is assigned a seven to eight digit study animal number by the PATH/TOX SYSTEM (PTS). This number consists of the PTS protocol number (first three to four digits) followed by the sequential animal number (e.g. XXXX0001). The Toxicology Technician will request (using the PATH/TOX SYSTEM) new cage identification labels which will include the following information: the study animal number, pre-test animal number, control article or compound number where appropriate, study number, cage number, sex, species, route and dose group. Cage identification labels will be mounted on cards color coded by dose group which will be laminated with plastic and attached to each cage. The color code is as follows: control - white, low dose - blue, intermediate dose - yellow, and high dose - red. Other colors may be used to identify additional groups and will be documented in an Instruction to Protocol, Study Memorandum or a Protocol Events Summary. For Exploratory studies, handwritten labels containing at least the following information may be used instead of computer-generated labels: control article or compound number, study number, sequential animal number and dose group.

For Acute studies, at the time of randomization, cages or polycarbonate boxes housing animals will be identified with a cage card containing at least the following information: study number, compound number, or control article, dose group, sequential animal number(s), sex, responsible technician, and responsible Study Director.

Before treatment initiation, animals will be tattooed on the tail with their assigned sequential animal number (optional for Exploratory studies). Each study animal will have the same number of digits (number, symbol or letter) tattooed on the tail for example 01-80 or M01-M80 if a separate satellite group(s) is used. The specifics regarding the tattoo procedure (e.g. number of digits used) will be documented on a Protocol Events Summary, General Procedures and Study Comments Form (# 7359), or a Tattoo Form (# 7610).

For Acute studies, before treatment initiation, animals will be tattooed as above. However, if a satellite group of animals is used, the sequential animal number for these satellite animals may be written on the tail with a permanent marker rather than tattooed.

DOGS, MONKEYS AND RABBITS

Animals are identified as described in Comparative Medicine Biology Support (CMBS) Standard Procedure 78-05.

GROTON, CT

STANDARD PROCEDURE

DRUG SAFETY EVALUATION

Section:	TOXICOLOGY
No.:	TOX-76-10
Effective:	June 1, 1999
Page:	3 of 3
Approved:	David L. Miffin 5/20/99
	Tammy Hughes 5/20/99
	Stanley Stasiuk 5-20-99

Supersedes: TOX-76-10 Dated April 3, 1995

Subject: RANDOMIZATION, IDENTIFICATION OF ANIMALS AND CAGES, AND CLEANING OF RACKS AND CAGES

Prior to randomization, cages housing animals will be identified with cards containing at least the following information: individual animal number (unique number assigned by CMBS), a sequential animal number, study number, compound number, sex and ACUP number (if multiple studies are housed in same room). Lamination of cage cards is recommended.

At the time of randomization, each study animal is assigned a seven to eight digit study animal number by the PATH/TOX SYSTEM (PTS). This number consists of the PTS protocol number (first three to four digits) followed by the sequential animal number (e.g. XXXX0001). The Toxicology Technician will generate new cage identification cards, which will include at least the following information: compound number (when appropriate), study number, the pre-study animal number (unique number assigned by CMBS), the sequential animal number, ACUP number (if multiple studies are housed in the same room), sex and dose group. Cage identification cards will be color coded by dose group, laminated with plastic and attached to each cage. The color code is as follows: control - white, low dose - blue, intermediate dose - yellow, and high dose - red. Other colors may be used to identify additional groups and will be documented in an Instruction to Protocol, Study Memorandum or a Protocol Events Summary.

IDENTIFICATION OF CAGE RACKS (RATS, MICE AND RABBITS)

All cage racks will be identified with at least the following information: a rack number (optional for Exploratory and Acute studies), compound number, study number, sex and ACUP number (if multiple studies are housed in the same room). Each rack (or its replacement) will remain in the same position in the room throughout the course of a study (optional for Exploratory and Acute studies).

CLEANING OF CAGE RACKS AND CAGES (RATS, MICE AND RABBITS)

At appropriate intervals (see table below) the Toxicology Technician (CMBS Technician for rabbits) will physically move animals from dirty into clean caging provided by CMBS personnel. Documentation of cage/rack changes will be made once prior to study initiation (e.g. in an Instruction to Protocol or Protocol Events Summary) specifying the cage change frequency. During the rack/cage change procedure each animal will be moved with its cage identification card; the cage sequence remains unchanged. Whenever water bottles are utilized, clean water bottles will be provided at least once weekly.

Cage/Rack Type	Species	Change Frequency
Hanging Wire	Rat	Every 2 weeks
Suspended Wire	Rabbit	Weekly
Polycarbonate box	Rat/Mouse	At least once weekly

EXHIBIT C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

INAD 10612 (E0002)

RECEIVED
JAN 31 2000
AHPD
REGULATORY AFFAIRS

JAN 21 2000

Robert Chesebrough
Manager, Regulatory Affairs
Pfizer Inc.
Eastern Point Road
P.O. Box 8010
Groton, CT 06340

Dear Mr. Chesebrough:

We refer to your submission dated November 10, 1999 (E0002), a proposed target animal safety drug tolerance test using UK-287,074 in dogs. UK-287,074 is a 3rd-generation cephalosporin antibiotic with an extended half-life proposed for subcutaneous injection in dogs with susceptible bacterial infections.

The protocol, entitled "Acute Safety Toleration of UK-287,074 in Dogs", is designed to test the safety of the drug at 10X for 10 days.

The protocol is acceptable as submitted with the following revisions. Suggested changes and/or additions to the protocol have been provided and may be used at your discretion. CVM's acceptance of a protocol indicates agreement that a study conducted in accordance with the protocol may reasonably be expected to test the study hypothesis. CVM can make no commitment that the data obtained from this protocol will actually support approval. We encourage submission of the final protocol to complete our file.

1. The duration of the acclimation period is not stated. Pre-study values are typically determined during a baseline period (after the acclimation period and before the administration of the drug). Please provide more information regarding the duration of the acclimation period and the timing of pre-study or pre-dose measurements.

2. Please list exclusion criteria for the study, if any (for instance, would abnormal pre-study lab values exclude a dog from the study?).

3. There is no mention of study blinding in the dog protocol. The cat protocol (I10613 E0002), however, does make provisions for blinding those involved in performing clinical evaluations/ physical exams and potentially histopathology to the treatment (UK-287,074 or placebo) group. Blinding those involved in assessing the dogs is preferred.

4. Likewise, the cat protocol states that clinical observations (to include vital signs) will be assessed several times the day of, as well as the day after, treatment initiation. We agree with that protocol, in that a qualified investigator should make several post-treatment assessments to include vital signs for the first 24 hours post-treatment (versus a more cursory general health observation by less qualified personnel).

5. The cat protocol also mentions in greater detail procedures for dealing with events like the death of a study animal. What will happen if death occurs in the dog study?

6. CVM's Target Animal Safety Guideline for New Animal Drugs (June 1989, Ch. III. Section B. Part a.) states that, "The market formulation of the drug should be used. If this is not possible, the formulation used should be acceptable for adequate testing of the product." Please provide additional information regarding the "commercial prototype" buffered solution intended for use in this study.

7. Part c.) of the same Guideline states, "For drugs intended for long-term, continuous use (15 days or longer), administer up to 10X the maximum proposed use level for up to 21 days." Observations from this study are proposed to last 10 days; there is some suggestion, from the Guideline comments above, and from information provided in the A0000 submission, that this drug, when administered at this dosage, will have the potential for clinically significant side effects well past 15 days. If you are considering longer-term label indications for this drug, we recommend extending the observation period to 21 days, and including at least one additional data point for lab values and physical exam findings.

8. Statistical evaluation of the data need only examine comparison of group means via a two-tailed t-test. The Dunnett's or Cochran-Cox t-tests are not necessary for a small, two-group study. The α value we use for toxicity studies is 0.1. Graphing responses to indicate trends would be helpful.

9. For statistical evaluation, it might be helpful to incorporate more quantitative food consumption observations. For instance, a measured or weighed amount of food (based on calculated maintenance energy requirements during stress) could be offered daily and the food measured/weighed a second time when removed from the run. The protocol as written does not mention the amount offered daily; it would be difficult even to estimate the amount eaten if different amounts are offered from day to day.

Future correspondence regarding this submission should be identified by the submission's correspondence date and our file number INAD 10612 (E0002). Submit all correspondence regarding this file directly to the Document Control Unit (HFV-199).

Should you have any questions or if we can be of further assistance please contact Dr. Tania D. Woerner, Acting Leader, Equine and Antimicrobial Drugs Team. The telephone number is (301) 827-0129.

Sincerely yours,

Linda Wilmot

Linda M. Wilmot, DVM
Acting Director
Division of Therapeutic Drugs for Non-Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

EXHIBIT D

Date of Approval: APR 2 5 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-285

CONVENIA

Cefovecin sodium
Injectable
Cats and Dogs

For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

For the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

Sponsored by:

Pfizer, Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION: CATS

A. File Number:	NADA 141-285
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	CONVENIA
D. Established Name(s):	Cefovecin sodium
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Injectable
G. Amount of Active Ingredient(s):	Each mL of reconstituted sterile injectable lyophile contains 80 mg of cefovecin as the sodium salt.
H. How Supplied:	CONVENIA is supplied as a multi-use vial equal to 80 mg/mL when reconstituted with 10 mL sterile water for injection.
I. How Dispensed:	Rx
J. Dosage(s):	CONVENIA should be administered as a single, one-time subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight. After an injection of CONVENIA, therapeutic concentrations are maintained for approximately 7 days for *Pasteurella multocida* infections.
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es):	cats
M. Indication(s):	For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

II. EFFECTIVENESS:

A. Dosage Characterization:

The minimum inhibitory concentrations (MICs) were determined for 45 clinical *Pasteurella multocida* isolates from infections in cats using applicable Clinical and Laboratory Standards Institute (CLSI) standards. The MIC value inhibiting 90% of isolates (MIC_{90}) was calculated. The MIC_{90} for *P. multocida* was ≤0.06 µg/mL. This value was used for the pharmacokinetic analyses used to support the dosage characterization of CONVENIA.

1. Binding of Cefovecin to Cat Plasma Proteins: *In Vitro* Binding of Cefovecin (UK-287,074) to Cat Plasma Proteins

This study (1680E-60-04-307) was conducted to determine the extent of *in vitro* binding of cefovecin to proteins in cat plasma. To estimate the relationship between free drug concentrations and the observed total cefovecin drug concentrations, the Hill function parameter values were estimated using SAS Proc NLIN. Using ln-transformed data for the estimated free and total drug concentrations, the fitted equation was:

$$\% \text{ Free} = 0.241 + 99.759 \, C_{total}^{8.01} / (C_{total}^{8.01} + 195.1^{8.01})$$

where 0.241 = C_0 = the asymptotic binding of cefovecin (% free) as total cefovecin concentrations approach zero, C_{total} = the measured total cefovecin concentration, 99.759 = (100 – C_0); 195.1 is the total cefovecin concentration at which the percent free = (100-C_0)/2; and 8.01 is the shape factor.

The percent protein binding in cat plasma was determined using equilibrium dialysis. The percent protein binding decreased in a nonlinear manner, ranging from 99.5% to 99.8% protein binding within the range of total plasma drug concentrations observed following a single 8 mg/kg injection to cats (10 – 100 µg/mL). Therefore, less than 0.5% of the total drug concentrations existed as free drug in the plasma. It is the free (unbound) drug that is available to exert antimicrobial effects.

2. Population Pharmacokinetics (PPK) of Cefovecin in Cats: Development of a Model and Simulation of Free Plasma Cefovecin Concentrations from the Intended Regimen

Data used in the development of the PPK model came from four studies and are summarized in Table 1.

Table 1: Summary of Subject Demographics for the Four Studies

Study	No. Cats	Sex	Age Range (yr)	BW Range (kg)
1580P-60-99-220	6	3 M / 3 F	1.02 – 1.18	2.55 – 6.35
1580E-60-03-301	6	3 M / 3 F	1.0 – 1.25	4.13 – 7.31
5582N-36-99-197	6	3 M/ 3 F	0.6 – 1.38	2.9 – 4.4
5881W-36-04-237	4	2 M/ 2 F	1.1 – 8.1*	3.0 – 6.5
Pooled Data	22	11 F/ 11 M	Generally Young Adult	2.55-7.31

* Three of the four cats in this study ranged in age from 1.1 – 2.1 yrs.

The plasma cefovecin concentration data were pooled from these studies based upon the following criteria:

- Treatment with a single subcutaneous (SC) dose of cefovecin at 6.7 – 9.8 mg/kg body weight
- Individually housed cats
- Serial blood sampling beginning no later than 4 hours after dosing and continuing for at least 21 days (at least 12 post-dose PK blood samples/cat).
- LC/MS/MS analytical methodology to determine total plasma cefovecin concentrations.

One of the above studies (Study 5582N-36-99-197) evaluated the PK of CONVENIA following IV and SC single-dose administration at 8 mg/kg, and determined the absolute bioavailability of CONVENIA following the SC dose. Table 2 shows the individual study values for the first period of SC administration.

Table 2: Feline Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (Mean ± Standard Deviation) Following Intravenous and Subcutaneous Administration of 8 mg/kg of Cefovecin in Cats

Parameter	Mean ± SD[I]
Terminal plasma elimination T (h)*[H]	166 (147, 190)
$AUC_{0\text{-}inf}$ (µg·h/mL)*[G]	22700 ± 3450
Time to maximum concentration, T_{max} (h)*[H]	2.0 ± 2.0
Maximum concentration, C_{max} (µg/mL)*[A]	141 ± 11.8
Vdss (L/kg)**[G]	0.090 ± 0.010
CL_{total} (mL/h/kg)**[G]	0.350 ± 0.40

[I] SD = standard deviation
* = Data from 6 subjects receiving a single subcutaneous dose of 8 mg/kg cefovecin
** = Data from 6 subjects receiving a single intravenous dose of 8 mg/kg cefovecin
A = arithmetic mean
H = harmonic mean (minimum estimated value, maximum estimated value)
G = geometric mean

The pooled plasma cefovecin concentration data from the above four studies resulted in a PPK dataset with 338 concentration records from 22 cats. Three of the four studies used an internal standard, cephalexin, which was added to the plasma samples before extraction. Study 1580P-60-99-220 did not use the internal standard. The precision and accuracy of the plasma analysis was shown to be similar across all four investigations.

Details regarding the PPK analysis are provided in the canine portion of this FOI summary. The model parameters generated in study 1680E-60-04-307 were used to estimate the percentage of free cefovecin through the range of anticipated total cefovecin plasma concentrations. Table 3 provides the PPK parameter values.

Table 3: Parameter Values from the Cat PPK Model

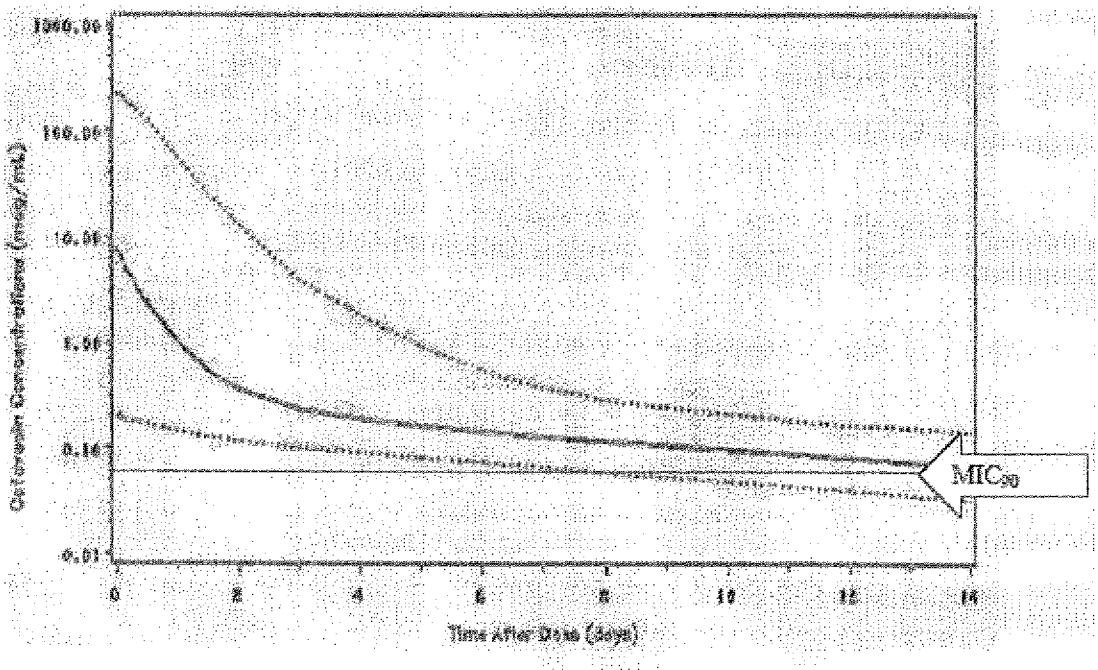
Parameter	Population Value (%SE)	95% Range of Values	Inter-Individual SD (% SE)*
CL/F (mL/h/kg)	0.293 (8.0)	0.256-0.334	0.342 (25.8)
Vp/F (mL/kg)	58.3 (7.2)	50.3-67.1	0.344 (24.8)
Vt/F (mL/kg)*	17.7 (10.5)	14.6-20.7	ND
Q/F (mL/h/kg)*	0.443 (38.8)	0.264-0.775	ND
SD of Residual Error	0.166 (8.1)	0.153-0.179	ND

* 95% range of values for Inter-Individual SD in CL/F and Vp/F = 0.232 – 0.427 and 0.226 – 0.430, respectively. Correlation between CL/F and Vp/F and 95% range of values = 0.919 and 0.823 – 0.974, respectively.

The individual parameter values generated during the successful parametric bootstrap simulations (498 data sets with 10,956 cats) were used to simulate (total) plasma cefovecin concentrations from a single 8 mg/kg SC dose. Free (unbound) cefovecin concentrations were estimated from the simulated total plasma cefovecin concentrations, based on the fit of a Hill function, to plasma protein binding data. Plasma protein binding data measured in an *in vitro* system using equilibrium dialysis were employed. SAS Proc NLIN was used to estimate the Hill function parameter values, and a SAS program was then used to estimate the time interval that the predicted free cefovecin concentrations remained above the minimum inhibitory concentration of the feline skin pathogen, *P. multocida*, which is associated with an MIC_{90} value of 0.06 µg/mL.

Figure 1 shows the modeled results of mean total and free concentration of cefovecin in plasma following a single subcutaneous injection of 8 mg/kg body weight in cats. The simulations indicated that > 95% of cats will have free plasma cefovecin concentrations ≥0.06 µg/mL for 7 days after an 8 mg/kg SC dose.

Figure 1: Predicted Free Concentrations of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Cats (Population Prediction and 90% Confidence Interval)



Conclusions: The PPK model, together with the MIC_{90} of the target pathogen, confirms that 95% of the potential feline patient population will have active (unbound) cefovecin plasma concentrations exceeding the MIC_{90} of the targeted pathogen (0.06 µg/mL) for approximately 7 days. This conclusion supports a dosage of 8 mg/kg body weight administered subcutaneously in cats, for the treatment of skin infections (wounds and abscesses) caused by the target pathogen (*P. multocida*).

3. Radiolabeled Cefovecin Study in Cats: Excretion of Radiolabel Following a Single Subcutaneous Dose of [14C]Cefovecin at 8 mg/kg to Cats.

   This study was conducted to determine the urinary and fecal excretion of radiolabel following a single subcutaneous dose of [14C]Cefovecin to cats and to estimate the total cefovecin residence time in the cat.

   Four male and four female cats received an 8 mg/kg dosage at a volume of 0.1 mL/kg. Following the radiolabeled dose, urine, feces, and plasma samples were collected.

   Based upon a ln-linear regression of the terminal portion of the concentration-time profile for the radio-labeled compound, the terminal elimination rate constant for cefovecin was observed to be 13 days in some cats.

   The results of the radiolabeled cefovecin study in cats indicate the potential persistence of cefovecin in the body. Based on the half life (T½ of 13 days) estimates provided in the radiolabel study, approximately 65 days is needed to eliminate 97% of the administered dose from the body.

B. Substantial Evidence:

The effectiveness of CONVENIA in the treatment of naturally occurring skin infections (wounds and abscesses) in cats presented as veterinary patients was evaluated in a controlled, masked study. CONVENIA was administered subcutaneously at the recommended dosage of 8 mg/kg in the commercial formulation. Twenty-six veterinary practices located in 13 States within the United States enrolled cats in this study.

1. Study Title: Efficacy and Safety of Cefovecin in the Treatment of Skin Infections in Cats Presented as Veterinary Patients

2. Type of Study: Multi-center, effectiveness study (GCP) involving 291 cats.

3. Investigators:

Susan Baker, DVM West Palm Beach, FL	Mildred Bass, DVM Farragut, TN
JoAnna Bender, DVM Rochester, NY	Brett Berryhill, DVM Baton Rouge, LA
Michael Bomar, DVM Wichita Falls, TX	Gary Brotze, DVM New Braunfels, TX
Bruce Coston, DVM Woodstock, VA	Bill Craig, DVM San Antonio, TX
Peter Davis, DVM Augusta, ME	Mark Girone, DVM Antioch, TN
William Greene, DVM Russ Anderson, DVM Nashville, TN	Larry Hendricks, DVM Germantown, TN
Theresa Hendrickson, DVM Manassas, VA	Stephen L. Jones, DVM Moncks Corner, SC
Charles Koenig, VMD Limerick, PA	Sharon Lachette, VMD White Haven, PA
William Lambert, DVM Milan, TN	John McCormick, DVM Nashville, TN
Ken McMillan, DVM Cropwell, AL	Susan Moon, DVM Memphis, TN
Dean Rund, DVM Springfield, MO	Roger Sifferman, DVM Springfield, MO
Brad Theodoroff, DVM Rochester Hills, MI	Gregory Tremoglie, VMD Glenmoore, PA
Carol Wolff, DVM Falmouth, ME	Philip Waguespack, DVM Baton Rouge, LA

4. General Design:

a. Purpose of Study: To confirm the effectiveness of CONVENIA against naturally occurring skin infections (wounds and abscesses) in cats when administered once, subcutaneously at 3.6 mg/lb (8 mg/kg) body weight.

b. Description of Test Animals: Two hundred and ninety-one (291) cats were randomly assigned to a single subcutaneous injection of 8 mg/kg CONVENIA (147 cats aged 2.4 months to 21 years) or 10 mg/lb cefadroxil administered orally once daily for 14 days. Four different pure and 5 different mixed breeds of cats were treated with CONVENIA.

c. Control and Treatment Group(s):

Table 4: Treatment Groups

Tx Group	Dose mg/kg	Number of cats enrolled (# evaluable)
cefovecin	3.6 mg/lb (8 mg/kg)	147 (89)
cefadroxil	10 mg/lb once daily orally	144 (88)

d. Inclusion Criteria: Cats enrolled in the study had a clinically significant skin infection characterized by a "moderate or severe" scoring of one or more of the following clinical signs at the time of enrollment: nodules, furuncles, erythema, purulent discharge and/or swelling. In addition, the presence of pathogenic bacteria was confirmed by microbiological culture via a sample collected from the infection site prior to treatment.

e. Exclusion Criteria: Cats not having a positive pre-treatment bacterial culture and cats not scoring at least one moderate/severe rating in the clinical categories were excluded from the study.

f. Dosage Form:

CONVENIA - Final market formulation CONVENIA was reconstituted with sterile water for injection prior to administration (80 mg/mL of cefovecin).

Cefadroxil - oral suspension 50 mg/mL

g. Route of Administration:

CONVENIA - subcutaneous injection
Cefadroxil - oral administration

To facilitate masking, cats allocated to the CONVENIA group also received an oral placebo and cats allocated to the cefadroxil group also received a placebo injection. Therefore, none of the individuals involved in the study (including but not limited to those individuals performing effectiveness assessments) were aware of the treatment groups.

h. Study Duration: 28 days

i. Variables Measured:

Effectiveness was assessed based on clinical signs of skin infection. Clinical signs were scored by the Examining Veterinarian as being absent, mild,

moderate, or severe on Days 0 (prior to treatment), 7, 14, and 28. At the time of the final assessment, the Examining Veterinarian also provided an evaluation of the overall clinical outcome of each case.

Baseline clinical pathology values (hematology, clinical chemistry, and urinalysis) were collected prior to treatment administration and at study end. Abnormal health observations and concurrent medications administered to each cat were recorded. In addition, any injection site abnormalities were recorded for each animal.

Microbiological cultures were obtained from each cat at the beginning of the study, and from any cat with a lesion (treatment failures) to culture at the end of the study.

j. Statistical Analysis:

A cat successfully completed the study if each clinical sign initially classified as moderate or severe was reduced to mild or absent by Day 28. The percentage of cats successfully treated was calculated at Day 14 and Day 28. Cats withdrawn from the study due to lack of effectiveness were considered treatment failures.

The determination of effectiveness was based on the number of cats successfully completing the study 28 days after initiation of treatment.

A per protocol population was defined for effectiveness analysis. The per protocol population consisted of cats that were randomized to treatment and met all of the inclusion criteria, none of the exclusion criteria, received at least one dose of either CONVENIA or cefadroxil and had sufficient observations for effectiveness evaluation.

A non-inferiority test was conducted for the percent of cases successfully treated in the two treatment groups and completing the study. Non-inferiority was concluded if the one-sided lower limit of the difference between percentages of successful completion was above the non-inferiority margin. This test was conducted on the per protocol population animals at a one-sided 5% significance level and a non-inferiority margin of 15 percentage points. A secondary non-inferiority analysis was conducted excluding those that missed three or more doses of cefadroxil.

5. Results:

There were 291 cats enrolled in the study. This included 147 CONVENIA cases and 144 cefadroxil cases. One hundred and fourteen cases (114) were excluded from the effectiveness evaluation. The most common reason for exclusion was failure to confirm a viable isolate during bacterial identification and minimum inhibitory concentration testing. Other reasons for exclusion were failure to meet

inclusion criteria, insufficient number of evaluable cases from a site, missing or incomplete microbiology data, and extreme scheduling deviations for the final assessment visit.

The effectiveness evaluation was based on 89 CONVENIA cases and 88 cefadroxil cases. This included eight cats that withdrew from the study prior to completion due to lack of effectiveness or adverse reactions. These cats were considered treatment failures.

The percentage of cats from evaluable cases (CONVENIA- and cefadroxil-treated) with clinical signs of skin infection (purulent discharge, swelling, erythema, nodules, and furuncles) is summarized in Table 5.

Table 5: Percentage of Cats with Clinical Signs of Skin Infections (Wounds and Abscesses)

Clinical Sign	Treatment	Day 0	Day 7	Day 14	Final Assessment (Day 28)
Purulent Discharge	CONVENIA	95.5	12.4	1.2	0.0
	cefadroxil	96.6	15.3	3.6	6.1
Swelling	CONVENIA	98.9	34.8	10.6	0.0
	cefadroxil	93.2	40.0	9.5	6.1
Erythema	CONVENIA	89.9	44.9	11.8	0.0
	cefadroxil	93.2	38.8	15.5	4.9
Nodules	CONVENIA	0.0	0.0	0.0	0.0
	cefadroxil	8.0	4.7	2.4	0.0
Furuncles	CONVENIA	2.2	0.0	0.0	0.0
	cefadroxil	4.5	3.5	1.2	1.2

Notes:
1. Includes all evaluable animals in the per protocol population
2. Actual study observation days for Day 0: -3 to 0, Day 7: 5 to 9, Day 14: 16 to 19, Day 28: 25 to 38.
3. Number of CONVENIA animals observed on Day 0: 89; Day 7: 89 Day 14: 85, Day 28: 81
   Number of cefadroxil animals observed on Day 0: 88; Day 7: 85 Day 14: 84, Day 28: 82
4. By Day 28 assessment, some cats were lost due to treatment failures, adverse reactions, and no final assessment.

Fourteen days after injectable treatment administration (Day 14), each clinical sign of skin infection had been reduced to mild or absent in 87/89 (97.8%) of CONVENIA-treated cats and in 84/88 (95.5%) of cefadroxil-treated cats.

Twenty-eight days after injectable treatment administration (Day 28), each clinical sign of skin infection had been reduced to mild or absent in 86/89 (96.6%) of CONVENIA-treated cats and in 80/88 (90.9%) of cefadroxil- treated cats.

Using a non-inferiority margin of 15%, CONVENIA was determined to be non-inferior to cefadroxil 28 days after injectable treatment (Table 6).

Based on the Examining Veterinarian's assessment of the overall clinical outcome of each case 28 days after injectable treatment, 85 (95.5%), 2 (2.2%), and 2 (2.2%) of the CONVENIA-treated cats and 77 (87.5%), 3 (3.4%) and 8 (9.0%) of the cefadroxil-treated cats were cured, improved or failed, respectively. One CONVENIA case was considered a treatment failure due to an adverse reaction, not lack of effectiveness. This cat was assessed by the veterinarian as a success based on clinical outcome. Refer to Table 6.

Table 6: Number and Percentage of Cats Successfully Treated During the Study

	Number (Percentage) of Cats Successfully Completing Study[1]			
	Day 14 Assessment		Day 28 Assessment (Final)	
Treatment	Yes	No	Yes	No
CONVENIA	87 (97.8%)	2 (2.2%)	86 (96.6%)[2]	3 (3.4%)
cefadroxil	84 (95.5%)	4 (4.5%)	80 (90.9%)[2]	8 (9.1%)

[1]Successful completion defined as reduction in the severity of the clinical signs of skin infection (purulent discharge, swelling, erythema, nodules, and furuncles) to mild or absent in severity.
[2]CONVENIA non-inferior to cefadroxil ($\delta = 0.15$).

a. Concomitant Treatments

A variety of concomitant medications were administered to cats concurrently with cefovecin. These included heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, and routine vaccinations.

b. Adverse Reactions:

Vomiting and diarrhea were the most common abnormal observations in both treatment groups. One CONVENIA cat was euthanized for testing positive for feline immunodeficiency virus.

A total of 291 cats were included in the field study safety analysis. Abnormal health observations reported in cats treated with CONVENIA and cefadroxil are summarized in Table 7.

Table 7: Number of Cats* with Adverse Reactions Reported During Field Study with CONVENIA		
Adverse Reaction	CONVENIA (n = 147)	cefadroxil (n = 144)
Vomiting	10	14
Diarrhea	7	26
Anorexia/Decreased Appetite	6	6
Lethargy	6	6
Hyper/Acting Strange	1	1
Inappropriate Urination	1	0

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

c. Injection Site Observations:

CONVENIA or injectable placebo was administered by the Examining Veterinarian subcutaneously at a site free of any pre-existing abnormalities and not near the sites of other injectable treatments. Injections were administered in five anatomical regions: thorax, forelimb, hind limb, dorsal scapula or lumbar region. The percentage of cefovecin-treated cats receiving treatment at each site are as follows: thorax 39%, left and right forelimb 23%, left and right hind limb 18%, dorsal scapula 11%, and lumbar 10%.

There were no abnormal injection site observations in CONVENIA-treated cats.

d. Clinical Pathology:

There were no notable differences between mean values for all laboratory tests among CONVENIA and cefadroxil-treated cats. For individual laboratory values, the following findings are noted:

There were 16 CONVENIA cases with decreased WBC counts post-study (< 5.5 X 10^{-3}/mm^3).

There were four CONVENIA cases with normal hematocrit values pre-study and decreased hematocrit values post-study. Another CONVENIA case had a pre-study hematocrit of 19.2% and a post-study hematocrit of 10.5%. This cat was 4.2 lbs and 8 months old. There is no follow up on this cat after Day 28.

Many CONVENIA cases had decreased pre-study and post-study platelet values. This is not an uncommon finding in cats due to the tendency for platelet clumping.

Four CONVENIA cases had elevated post-study ALT (alanine aminotransferase) levels (normal range = 0 – 120 IU/L). One case was elevated pre-study.

There were 24 CONVENIA cases with normal pre-study BUN (blood urea nitrogen, normal range = 10 - 30 mg/dL) values and elevated post-study BUN values (ranging from 37 – 39 mg/dL post-study).

There were six CONVENIA cases with normal pre- and elevated post-study creatinine values (normal range = 0.8 – 2.0 mg/dL). Two of these cases also had an elevated post-study BUN.

There were 10 CONVENIA cases with elevated post-study calcium levels (normal range 8.8 – 11.0 mg/dL). It is noted that the post-study albumin levels were high for seven of these cases.

None of the animals showed clinical signs associated with these laboratory changes.

e. Microbiology:

CONVENIA is a cephalosporin antibiotic. Like other β-lactam antimicrobials, CONVENIA exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalently binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall.

Identification of bacterial pathogens was made to the species level, based on morphology, Gram stain, growth characteristics, standard individual biochemical testing and/or commercially available identification test kits. Minimum inhibitory concentration (MIC) testing was conducted in accordance with applicable Clinical and Laboratory Standards Institute (CLSI) standards. CONVENIA MICs for the pre-treatment bacterial pathogens isolated from enrolled cats are summarized in Table 8.

Table 8: Activity of CONVENIA Against Pathogens Isolated from Cats Treated With CONVENIA in Field Studies in the U.S. During 2001-2003

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Skin infections	*Pasteurella multocida*	Success	57	Pre-Treatment	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12
		Failure	1	Pre-Treatment			≤ 0.06

6. Conclusions:

CONVENIA administered as a single subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight was effective against naturally occurring skin infections (wounds and abscesses) in cats against susceptible strains of *Pasteurella multocida*.

III. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Michael C. Savides, PhD.
Ricerca, LLC
Concord, OH

3. General Design:

a. Purpose: To determine the toxic effects of CONVENIA when administered once subcutaneously to cats at an exaggerated dose (180 mg/kg body weight).

b. Test Animals: Twelve healthy cats (6M and 6F), approximately 7 months of age, were randomly assigned to either CONVENIA or the control group (three/sex/group).

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: Dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for the Drug Tolerance Study

Group	Dose mg/kg	Number and Sex of Cats
1	0 mg/kg (saline)	3 males, 3 females
2	180 mg/kg	3 males, 3 females

g. Test duration: Thirty days

h. Variables measured: Clinical observations, physical exams, injection site evaluations, body weight, hematology, serum chemistry, coagulation tests, plasma drug concentrations, urinalysis, and food consumption were assessed.

4. Results: All cats survived to termination of the study.

a. Abnormal clinical findings included vocalization and scratching. Edema associated with the CONVENIA injection sites occurred within two hours of the administration. All edema resolved within eight hours of the CONVENIA injection.

b. Hematology and serum chemistry: The mean WBC counts were lower in the cefovecin group (mean WBC = 10.93) than in the control group (mean WBC = 14.48) at Day 10. All mean WBC counts remained within the normal range[1] [5.5-19.5 X 10^3/mm^3 for the study lab].

c. Urinalysis: One cat in the CONVENIA group had a small amount of bilirubinuria on Day 10.

d. Plasma drug concentrations: In both the male and female cats, concentrations of CONVENIA were greatest at the initial sampling time (1.5 hours), and remained above the limit of detection (0.05 mcg/mL) for the duration of the study. These data indicate that cefovecin was rapidly absorbed and has a prolonged time for elimination from the plasma.

5. Conclusions: Under the conditions of this study, the cats remained healthy throughout the 30-day study duration. Irritation immediately following injection and transient injection site edema occurred within two hours of administration. All edema resolved within eight hours.

[1] Duncan, J.R., Prasse, K.W., and Mahaffey, E.A. 1994. Veterinary Laboratory Medicine, Third Edition. Iowa State University Press, Ames.

B. Margin of Safety and Injection Site Tolerance of Cefovecin Injectable Solution in Cats:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Elizabeth Evans, DVM
Midwest Research Institute (MRI)
Kansas City, MO

3. General Design:

a. Purpose: To evaluate the safety and injection site toleration of CONVENIA when administered subcutaneously, once every 7 days for a total of five injections in cats.

b. Test Animals: Thirty-two healthy cats (16M and 16F), approximately 12-16 weeks of age, were randomly assigned to the four dose groups.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: Dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for Safety Study

1) Control (saline) every seven days for four consecutive weeks (5 total doses)
2) 12 mg/kg (1.5 X) every seven days for four consecutive weeks (5 total doses)
3) 36 mg/kg (4.5 X) every seven days for four consecutive weeks (5 total doses)
4) 60 mg/kg (7.5 X) every seven days for four consecutive weeks (5 total doses)

g. Test duration: Forty-two days

h. Variables measured: Evaluations included clinical signs, general health observations, physical examinations, body weight, hematology, coagulation tests, serum chemistry, urinalysis, fecal examination, gross pathology and histopathology, injection site evaluations, and plasma blood concentrations.

4. Results: All cats survived to termination of the study.

a. Clinical observations: Soft, thickened palpable lesions (1/2 cm or less) were associated with the injection sites of the control and CONVENIA-treated cats. Most injection site swellings occurred within one hour of administration. The largest (width X length) swelling noted for the injection sites was 3 mm X 3 mm. This was seen in one cat in the 36 mg/kg group and two cats in the 60

mg/kg group. The occurrence of injection site swellings increased with the number of injections given. Irritation and vocalization occurred in some cats following administration of high doses. There were a statistically significant greater number of cats ($p < 0.1$) in the 60 mg/kg group compared to the controls with injection site swellings after the 3rd and 4th injections. See Table 9 below. All swellings resolved within 12 hours of drug administration.

Table 9: Number of Cats/Group with Injection Site Swelling

	Control	12 mg/kg	36 mg/kg	60 mg/kg
1st injection	0	0	1	2
2nd injection	0	1	3	1
3rd injection	0	1	2	4*
4th injection	3	3	7	8*
5th injection	3	4	5	7

* $p < 0.1$, statistically significant

Lip lesions consistent with eosinophilic granulomas were seen in all four study groups throughout the study. Incidences of vomiting and diarrhea increased with increasing dose. Diarrhea often lasted three or more days following injections in the 60 mg/kg group.

b. Hematology and serum chemistry: There was a trend toward decreasing mean neutrophil percentage values seen with increasing dose.

The mean albumin levels for the CONVENIA groups were significantly lower than the control group for all in-study time points ($p < 0.01$ for time points 1, 2, 3, and 4; and $p < 0.05$ at time point 5). All means remained within the normal reference range for this lab [normal range = 2.5 - 3.9 gm/dL]. See Table 10.

Table 10: Mean Albumin Values at In-Study Time Points

	Mean albumin value (gm/L)			
Time Point	Control group	12 mg/kg group	36 mg/kg group	60 mg/kg group
Day 6 - 7	3.450	3.112	2.95	2.95
Day 12 - 13	3.475	3.213	3.113	3.075
Day 19 - 21	3.488	3.038	3.038	3.025
Day 26 - 28	3.600	3.238	3.150	3.050
Day 40 - 41	3.613	3.413	3.40	3.425

The mean alkaline phosphatase values were significantly higher ($p = 0.0291$) for the 60 mg/kg group compared to the control group over all time points [normal alkaline phosphatase range for this lab = 0 - 90 IU/L]. See Table 11.

Table 11: Mean Alkaline Phosphatase Values at In-Study Time Points

	Mean alkaline phosphatase value (IU/L)	
Time Point	Control group	60 mg/kg group
Day -8-1	93.75	118.125
Day 6-7	96.75	128.125
Day 12-13	90.75	117.125
Day 19-21	89.75	132.375
Day 26-28	91.125	138.250
Day 40-41	86.375	124.625

c. Pathology: Two cats in the 60 mg/kg group had small serosal to mucosal lesions (2 mm) in the duodenum. These two cats also exhibited diarrhea. This lesion also occurred in one control cat (no clinical signs of diarrhea). One cat in the 12 mg/kg group had a fibrotic kidney lesion of the tubules and interstitium. Another cat in this 12 mg/kg group showed mild glomerulosclerosis in one kidney. The relationship to drug administration could not be determined.

   Hepatic lesions included minimal liver vacuolation in a 12 mg/kg cat, moderate liver vacuolation in one 36 mg/kg group cat, and one cat in the 36 mg/kg group with minimal liver inflammation.

   Histopathological changes noted at the injection sites were minimal and included perivascular inflammation and minimal granulomatous, parafollicular inflammation.

d. Plasma drug concentrations: A less than dose proportional change in total drug exposure was seen as doses increased from 12 mg/kg to 60 mg/kg in cats. Accordingly, total drug peak and trough concentrations of CONVENIA in plasma were similar in cats receiving subcutaneous doses of 12 mg/kg, 36 mg/kg, and 60 mg/kg of CONVENIA. Concentrations were generally similar between male and female cats.

5. Conclusions: CONVENIA administered once every seven days for four consecutive weeks, at doses up to 60 mg/kg body weight did not produce toxicity in healthy cats. The relationship between mild renal and hepatic lesions and CONVENIA administration is not clear. Irritation and vocalization occurred following high dose administration in some cats. Edema at the injection sites resolved within 12 hours. Increased incidences of vomiting and diarrhea were associated with 36 mg/kg and 60 mg/kg doses of CONVENIA.

IV. GENERAL INFORMATION: DOGS

A. File Number:	NADA 141-285
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	CONVENIA
D. Established Name(s):	Cefovecin sodium
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Injectable
G. Amount of Active Ingredient(s):	Each mL of reconstituted sterile injectable lyophile contains 80 mg of cefovecin as the sodium salt.
H. How Supplied:	CONVENIA is supplied as a multi-use vial equal to 80 mg/mL when reconstituted with 10 mL sterile water for injection.
I. How Dispensed:	Rx
J. Dosage(s):	CONVENIA should be administered as a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) body weight. A second subcutaneous injection of 3.6 mg/lb (8 mg/kg) may be administered if response to therapy is not complete. The decision for a second injection for any individual dog should take into consideration such factors as progress toward clinical resolution, the susceptibility of the causative organisms, and the integrity of the dog's host-defense mechanisms. Therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections. Maximum treatment should not exceed 2 injections.
K. Route(s) of Administration:	Subcutaneous injection

L. **Species/Class(es):** Canine

M. **Indication(s):** For the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

V. EFFECTIVENESS:

A. Dosage Characterization:

The minimum inhibitory concentrations (MICs) were determined for 69 clinical bacterial isolates from infections in dogs using applicable Clinical and Laboratory Standards Institute (CLSI) standards. MIC values inhibiting 90% of *Staphylococcus intermedius* and *Streptococcus canis* isolates (MIC_{90}) were calculated. The MIC_{90} for *Staphylococcus intermedius* was 0.25 µg/mL and for *Streptococcus canis* was ≤0.06 µg/mL. These values were used for the pharmacokinetic analyses used to support the dosage characterization of CONVENIA in dogs.

1. Binding of Cefovecin to Dog Plasma Proteins: *In Vitro* Binding of Cefovecin (UK-287,074) to Dog Plasma Proteins

   This study was conducted to determine the extent of *in vitro* binding of cefovecin to proteins in dog plasma. To estimate the relationship between free drug concentrations and the observed total cefovecin drug concentrations, the Hill function parameter values were estimated using SAS Proc NLIN. The resulting fitted equation was:

   $$\% \text{ Free} = 1.39 + 98.61\ C_{total}^{4.39} / (C_{total}^{4.39} + 184^{4.39})$$

   where $1.39 = C_0$ = the asymptotic binding of cefovecin (% free) as total cefovecin concentrations approach zero, C_{total} = the measured total cefovecin concentration, $98.61 = (100 - C_0)$; 184 is the total cefovecin concentration at which the percent free = $(100\text{-}C_0)/2$; and 4.39 is the shape factor.

   The percent protein binding in dog plasma was determined using equilibrium dialysis. The percent protein binding decreased in a nonlinear manner, ranging from 96% to 98.7% protein binding within the range of total plasma drug concentrations observed following a single 8 mg/kg injection to dogs (10 – 100 µg/mL). By Day 2 post-dose, less than 2% of the total drug concentrations existed as free drug in the plasma. It is the free (unbound) drug that is available to exert antimicrobial effects.

2. Population Pharmacokinetics (PPK) of Cefovecin in Dogs: Development of a Model and Simulations to Predict Free Plasma Cefovecin Concentrations from the Intended Therapeutic Regimens

Data used in the development of the PPK model came from seven studies and are summarized in Table 12.

Table 12: Summary of Subject Demographics for the Seven Studies

Study	No. Dogs	Sex	Age Range (mo)	BW Range (kg)
5562N-36-99-210	6	3F/3M	11.6 – 16.5	11.4 - 15.3
5561C-36-00-218	12	5F/7M	10.5 – 25.5	12.7 – 16.9
5560E-36-01-236	3	3F/0M	>10†	10.0 – 20.0†
1560P-60-99-368	4	2F/2M	18.6 – 20.2	9.7 – 12.1
1560E-60-00-466	4	2F/2M	8.9 – 9.3	9.1 – 13.5
1560N-60-01-500	4	2F/2M	19 - 19	5.5 – 10.2
1560E-60-03-657	6	3F/3M	Adults†	6.7 - 9.6
Pooled Data	39	20F/19M	Generally Young Adult	5.5 – 20.0

†Protocol specified inclusion/exclusion criteria

The plasma cefovecin concentration data were pooled from these studies. Other common features of the seven studies included:

- Commercial prototype formulation
- At least 10 serial blood samples/dog for determination of plasma cefovecin concentrations with sampling beginning no later than four hours after dosing and continuing for at least 504 hours.
- LC/MS/MS analytical methodology to determine total plasma cefovecin concentrations

One of the above studies (Study 5562N-36-99-210) evaluated the PK of CONVENIA following IV and SC single-dose administration at 8 mg/kg, and determined the absolute bioavailability of CONVENIA following the SC dose. Table 13 shows the individual study values for the first period of SC administration.

Table 13: Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (mean ± standard deviation) Following Intravenous and Subcutaneous Administration of 8 mg/kg of Cefovecin in Dogs

Parameter	Mean ± SD[1]
Terminal plasma elimination T (h)*[H]	133 (96, 206)
$AUC_{0\text{-}inf}$ (µg·h/mL)*[G]	10400 ± 1900[P]
Time to maximum concentration, T_{max} (h)*[H]	6.2 ± 3.0
Maximum concentration, C_{max} (µg/mL)*[A]	121 ± 51
Vdss (L/kg)**[G]	0.122 ± 0.011
CL_{total} (mL/h/kg)**[G]	0.76 ± .0.13[P]

[1] SD = standard deviation
p = a phase effect was observed, only data for the first phase are provided (n=6); all other data provided are derived from 12 animals
* = SC
** = IV
A = arithmetic mean
H = harmonic mean (minimum estimated value, maximum estimated value)
G = geometric mean

The pooled plasma samples from the 7 studies (591 concentration records) were analyzed using a sensitive and specific HPLC method with tandem mass spectrometric detection (LC/MS/MS). Five of the seven studies used an internal standard, cephalexin, which was added to the plasma samples before extraction; two studies did not use an internal standard. The precision and accuracy of the plasma analysis was shown to be similar across all seven investigations.

The program NONMEM version 6 was used to fit various PPK models to the data and to perform simulations to evaluate the stability of the final model. A two-compartment linear population pharmacokinetic model with a proportionate error structure was found to adequately describe the data. Structural model parameters were the population values of the 1st order absorption rate constant (Ka), total body plasma clearance (CL/F), the apparent volumes of distribution of the central and peripheral compartments (Vp/F, Vt/F, respectively), and the inter-compartmental clearance (Q/F). Inter-individual variability was estimated for CL/F and Vp/F, but not for any other parameters. A parametric bootstrap method was used to demonstrate the stability of the model, the accuracy of the model parameter values, and to obtain approximate confidence ranges for the parameters. Parameter values from the final model are listed in Table 14.

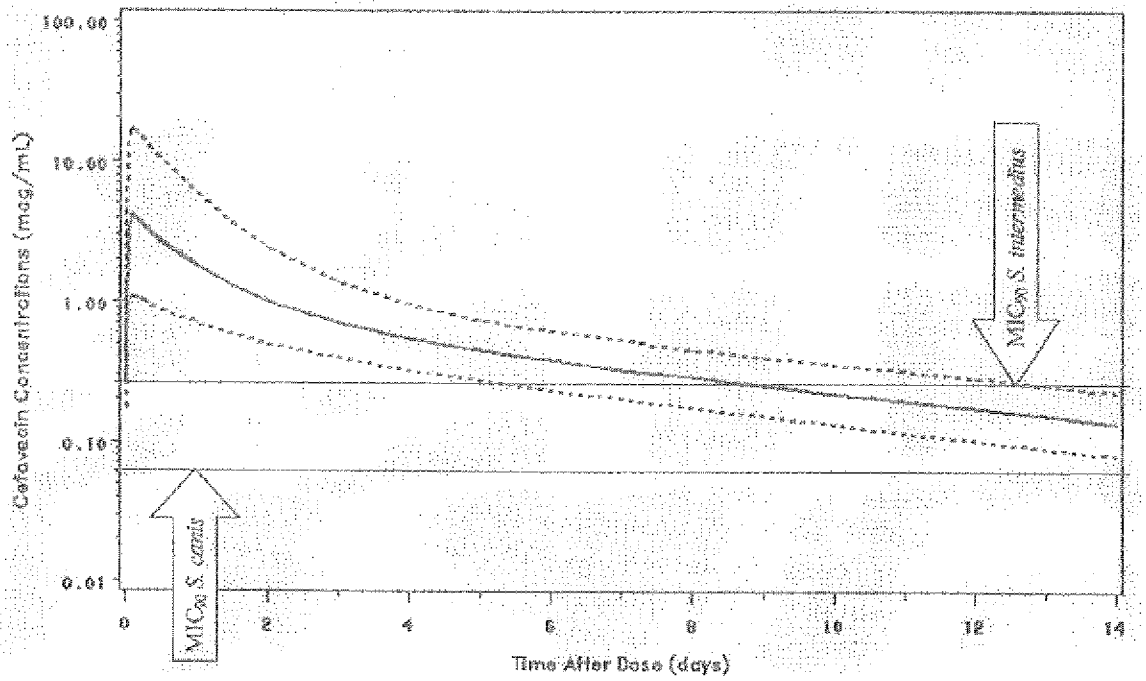
Table 14: Parameter Values for Final PPK Model

Parameter	Population Value (%SE)	95% Range of Values	Inter-Individual SD (% SE)
CL/F (mL/h/kg)	0.649 (2.7)	0.620 – 0.685	0.121 (33.9)
Vp/F (mL/kg)	90.2 (2.5)	86.0 – 95.7	0.145 (24.2)
Vt/F (mL/kg)*	27.9 (6.8)	24.1 – 31.4	ND
Q/F (mL/h/kg)*	0.410 (14.6)	0.294 – 0.557	ND
Ka (1/h)	2.56 (8.7)	2.20 – 3.01	ND
Correlation between CL/F and Vp/F	0.695 (ND)	0.451 – 0.881	ND
SD of Residual Error	0.192 (6.1)	17.8 – 20.4	ND

The individual parameter values generated during the successful parametric bootstrap simulations (499 data sets with >19000 dogs) were used to simulate (total) plasma cefovecin concentrations from two 8 mg/kg SC doses separated by either 7 or 14 days. Free (unbound) cefovecin concentrations were estimated from the simulated total plasma cefovecin concentrations, based on the fit of a Hill function to plasma protein binding data. Plasma protein binding data measured in an *in vitro* system using equilibrium dialysis were employed. SAS Proc NLIN was used to estimate the Hill function parameter values, and a SAS program was then used to estimate the time interval that the predicted free cefovecin concentrations remained above the minimum inhibitory concentration of the two indicated canine skin pathogens; MIC_{90} values of 0.25 µg/mL (*Staphylococcus intermedius*) or 0.06 µg/mL (*Streptococcus canis*) were used.

Figure 2 shows the modeled results of mean total and free concentration of cefovecin in plasma following a single subcutaneous injection of 8 mg/kg body weight in dogs. The simulations indicated that > 98% of dogs will have free plasma cefovecin concentrations ≥0.06 µg/mL for 14 days after an 8 mg/kg subcutaneous (SC) dose. Approximately 92% of dogs are predicted to have free plasma cefovecin concentrations ≥0.25 µg/mL for 6 days after an 8 mg/kg SC dose. Approximately 82 - 84% of dogs are predicted to have free plasma cefovecin concentrations ≥0.25 µg/mL at 7 days after the 8 mg/kg SC dose.

Figure 2. Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Dogs (Population Prediction and 90% Confidence Interval)



Conclusion: The PPK model, together with the MIC_{90} of the target pathogens, confirms that free cefovecin concentrations exceeded the MIC_{90} of *Staphylococcus intermedius* (0.25 µg/mL) for 7 days in approximately 82 - 84% of dogs and the MIC_{90} of *Streptococcus canis* (0.06 µg/mL) for 14 days in > 95% of dogs. Thus, therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections.

B. Substantial Evidence:

The effectiveness of CONVENIA in the treatment of naturally occurring skin infections (superficial secondary pyoderma, abscesses, and infected wounds) in dogs presented as veterinary patients was evaluated in a well-controlled, masked field study. CONVENIA was administered subcutaneously at the recommended dose of 8 mg/kg in the commercial formulation. Twenty-six veterinary practices located in 13 States within the United States enrolled patients in this study.

1. Study Title: Efficacy and Safety of Cefovecin in the Treatment of Skin Infections in Dogs Presented as Veterinary Patients

2. Type of Study: Multi-center, effectiveness study (GCP) involving 320 dogs.

3. Investigators:

Susan Baker, DVM West Palm Beach, FL	Mildred Bass, DVM Farragut, TN
JoAnna Bender, DVM Rochester, NY	Brett Berryhill, DVM Baton Rouge, LA
Michael Bomar, DVM Wichita Falls, TX	Gary Brotze, DVM New Braunfels, TX
Bruce Coston, DVM Woodstock, VA	Bill Craig, DVM San Antonio, TX
Peter Davis, DVM Augusta, ME	Mark Girone, DVM Antioch, TN
William Greene, DVM Russ Anderson, DVM Nashville, TN	Larry Hendricks, DVM Germantown, TN
Theresa Hendrickson, DVM Manassas, VA	Stephen L. Jones, DVM Moncks Corner, SC
Charles Koenig, VMD Limerick, PA	Sharon Lachette, VMD White Haven, PA
William Lambert, DVM Milan, TN	John McCormick, DVM Nashville, TN
Ken McMillan, DVM Cropwell, AL	Susan Moon, DVM Memphis, TN
Dean Rund, DVM Springfield, MO	Ralph Schoemann, DVM Guilford, CT
Roger Sifferman, DVM Springfield, MO	Brad Theodoroff, DVM Rochester Hills, MI
Gregory Tremoglie, VMD Glenmoore, PA	Carol Wolff, DVM Falmouth, ME

4. General Design:

a. Purpose of Study: To confirm the effectiveness of CONVENIA against naturally occurring skin infections (superficial secondary pyoderma, abscesses, and infected wounds) in dogs when administered subcutaneously at 3.6 mg cefovecin/lb body weight (8 mg/kg) once, or twice, 14 days apart, for a total of two treatments.

b. Description of Test Animals: Three hundred and twenty (320) dogs were randomly assigned to a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) CONVENIA (157 dogs - aged 8 weeks to 19 years) or 10 mg/lb (22 mg/kg) cefadroxil (163 dogs - aged 10 weeks to 15 years) administered orally twice daily for 14 days. At the discretion of the examining veterinarian, a second injection of CONVENIA or a second 14-day course of cefadroxil was initiated 14 days after the initial treatment. Fifty different pure and 24 different mixed breeds of dogs were treated with CONVENIA.

c. Control and Treatment Group(s):

Table 15: Treatment Groups

Treatment Group	Dose	Number of dogs enrolled (# evaluable)
CONVENIA	3.6 mg/lb (8 mg/kg)	157 (118)
cefadroxil	10 mg/lb (22 mg/kg) once daily orally	163 (117)

d. Inclusion Criteria: Dogs enrolled in the study had a clinically significant skin infection characterized by a "moderate or severe" scoring of one or more of the following clinical signs at the time of enrollment: papules, pustules, nodules, furuncles, erythema, erosion/ulceration, purulent discharge, and/or swelling. In addition, the presence of pathogenic bacteria was confirmed by microbiological culture via a sample collected from the infection site prior to treatment.

e. Exclusion Criteria: Dogs not having a positive pre-treatment bacterial culture and dogs not scoring at least one moderate/severe rating in the clinical categories were excluded from the study.

f. Dosage Form:

CONVENIA - Final market formulation cefovecin was reconstituted with sterile water for injection prior to administration (80 mg/mL of cefovecin).

Cefadroxil – oral tablets or oral suspension

g. Route of Administration:

CONVENIA - subcutaneous injection

Cefadroxil - oral administration

To facilitate masking, dogs allocated to the CONVENIA group also received an oral placebo and dogs allocated to the cefadroxil group also received a placebo injection. Therefore, none of the individuals involved in the study (including but not limited to those individuals performing effectiveness assessments) were aware of the treatment groups.

h. Study Duration: 28 days, 42 days for those dogs requiring a second course of treatment

i. Variables Measured:

Effectiveness was assessed based on clinical signs of skin infection. Clinical signs were scored by the examining veterinarian as being absent, mild, moderate, or severe on Days 0 (prior to treatment), 7, 14, 28, and 42. At the time of the final assessment, the examining veterinarian also provided an evaluation of the overall clinical outcome of each case.

Baseline clinical pathology values (hematology, clinical chemistry, and urinalysis) were collected prior to treatment administration and at study end. Abnormal health observations and concurrent medications administered to each dog were recorded. In addition, any injection site abnormalities were recorded for each animal.

Microbiological cultures were obtained from each dog at the beginning of the study, and from any dog with a lesion to culture at the end of the study (treatment failures).

j. Statistical Analysis:

A dog successfully completed the study if each clinical sign initially classified as moderate or severe was reduced to mild or absent at the final assessment. The percentage of dogs successfully treated was calculated 28 days after administration of the final treatment. Dogs withdrawn from the study due to lack of effectiveness or adverse reactions were considered treatment failures.

The determination of effectiveness was based on the number of dogs successfully completing the study 28 days after administration of the final treatment.

A per protocol population was defined for effectiveness analysis. The per protocol population consisted of dogs that were randomized to treatment and met all of the inclusion criteria, none of the exclusion criteria, received at least one dose of either CONVENIA or cefadroxil and had sufficient observations for effectiveness evaluation.

A non-inferiority test was conducted for the percent of cases successfully treated in the two treatment groups. Non-inferiority was concluded if the one-sided lower limit of the difference between percentages of successful completion was above the non-inferiority margin of 15 percentage points. This test was conducted on the per protocol population of dogs at a one-sided 5% significance level. A secondary non-inferiority analysis was conducted excluding those cases that missed three or more doses of cefadroxil.

5. Results:

There were 320 dogs enrolled in the study. This included 157 CONVENIA cases and 163 cefadroxil cases. Eighty-five cases (85) were excluded from the effectiveness evaluation. The most common reason for exclusion was failure to confirm a viable isolate during bacterial identification and minimum inhibitory concentration testing. Other reasons for exclusion were failure to meet inclusion criteria, insufficient number of evaluable cases from a site, missing or incomplete microbiology data, and extreme scheduling deviations for the final assessment visit.

The effectiveness evaluation was based on 118 CONVENIA-treated cases and 117 cefadroxil-treated cases. This included twelve dogs (6 from each treatment group) that withdrew from the study prior to completion due to lack of effectiveness or adverse reactions. These dogs were considered treatment failures.

Among all enrolled dogs, 22 of 157 dogs in the CONVENIA group received two treatments, and 35 of 163 dogs in the cefadroxil group received two courses of treatment. Among the evaluable cases, 17 of 118 dogs in the CONVENIA group received two treatments and 26 of 117 dogs in the cefadroxil group received two courses of treatment.

The percentage of dogs from evaluable cases (CONVENIA- and cefadroxil-treated) with clinical signs of skin infection at each evaluation time point (based on each individual clinical sign) is summarized in Table 16.

Table 16: Percentage of Dogs with Clinical Signs of Skin Infections

Clinical Sign	Treatment	Day 0	Day 7	Day 14	Final Assessment
Erosion/ulceration	CONVENIA	55.9	29.6	9.6	3.6
	cefadroxil	53.8	34.5	13.2	3.6
Erythema	CONVENIA	92.4	49.6	16.7	9.0
	cefadroxil	92.3	49.1	28.9	5.5
Furuncles	CONVENIA	7.6	1.7	0.9	0.0
	cefadroxil	12.8	3.4	2.6	0.9
Nodules	CONVENIA	10.2	3.5	0.0	0.0
	cefadroxil	12.8	5.2	2.6	0.0
Papules	CONVENIA	33.9	16.5	6.1	5.4
	cefadroxil	40.2	26.7	12.3	4.5
Purulent discharge	CONVENIA	68.6	12.2	5.3	2.7
	cefadroxil	73.5	12.9	6.1	0.9
Pustules	CONVENIA	39.8	9.6	7.0	4.5
	cefadroxil	46.2	20.7	8.8	5.5
Swelling	CONVENIA	66.9	31.3	13.2	3.6
	cefadroxil	69.2	35.3	9.6	1.8

Notes:
1. Includes all evaluable dogs in the per protocol population
2. Actual study observation days for Day 0: -3 to 0, Day 7: 5 to 10, Day 14: 11 to 18, Final Assessment: Day 19 to 38 for dogs that received a single treatment and Day 36-51 for dogs that received two treatments.
3. Number of CONVENIA dogs observed on Day 0: 118; Day 7: 115 Day 14: 114, Final Assessment: 111
   Number of cefadroxil dogs observed on Day 0: 117; Day 7: 116 Day 14: 114, Final Assessment: 110
4. Some dogs were lost to failures, adverse events, and missed visits.

The percentage of dogs from evaluable cases (CONVENIA- and cefadroxil-treated) cured (each clinical sign reduced to absent) at each evaluation time point by clinical diagnosis (abscess, folliculitis, or wound) is summarized in Table 17.

Table 17: Percentage of Dogs Cured by Clinical Diagnosis

Diagnosis	Treatment	Number of Dogs	Number (Percentage[1]) of Dogs Cured		
			Day 7	Day 14	Final Assessment
Abscess	CONVENIA	29	25 (89.3)	29 (100)	27 (93.1)
	Cefadroxil	25	21 (84.0)	24 (96.0)	24 (96.0)
Folliculitis	CONVENIA	62	53 (86.9)	56 (91.8)	57 (91.9)
	Cefadroxil	67	56 (84.8)	57 (89.1)	60 (89.5)
Wound	CONVENIA	27	21 (77.8)	25 (96.1)	25 (92.6)
	Cefadroxil	25	22 (88.0)	23 (92.0)	24 (96.0)
All	CONVENIA	118	99 (85.3)	110 (94.8)	109 (92.4)
	Cefadroxil	117	99 (85.3)	104 (91.2)	108 (92.3)

Notes:

1. Percentages are based on the actual number of dogs who returned for each visit. Dogs who withdrew for apparent lack of effectiveness are counted as failures on the scheduled visits.
2. Number CONVENIA dogs observed on Day 7: 116, Day 14: 116, Final Assessment: 118. Number of cefadroxil dogs observed on Day 7: 116, Day 14: 114, Final Assessment: 117.
3. Final assessment conducted on Day 28 for dogs receiving a single treatment and on Day 42 for dogs receiving two treatments.

Twenty-eight days after initiation of the final 14-day treatment, each clinical sign of skin infection had been reduced to mild (improved) or absent (cured) in 109 (92.4 %) of CONVENIA-treated dogs and in 108 (92.3%) of cefadroxil-treated dogs.

Using a non-inferiority margin of 15%, CONVENIA was determined to be non-inferior to cefadroxil 28 days after the final injectable treatment (Table 18).

Table 18: Number and Percentage of Dogs Successfully Treated During the Study

	Number (Percentage) of Dogs Successfully Treated and Completing Study[1]	
	Final Assessment	
Treatment	Yes	No
CONVENIA	109 (92.4%)[2]	9 (7.6%)
cefadroxil	108 (92.3%)[2]	9 (7.7%)

[1] Successful completion defined as reduction in the severity of clinical signs of skin infection to mild or absent in severity.

[2] CONVENIA non-inferior to cefadroxil ($\delta = 0.15$).

Based on the clinical outcome of each case 28 days after the final injectable treatment, in the CONVENIA treatment group there were 97 (82.2%) cures, 12

(10.2%) improvements, and 9 (7.6%) failures. In the cefadroxil treatment group there were 98 (83.8%) cures, 10 (8.5%) improvements, and 9 (7.7%) failures.

a. Concomitant Treatments

A variety of medications were administered to dogs concurrently with cefovecin. These included, but were not limited to, heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, routine immunizations, antihistamines, thyroid hormone supplementation, and non-steroidal anti-inflammatory agents.

b. Adverse Reactions:

Vomiting, diarrhea, decreased appetite, and lethargy were the most common abnormal observations in both treatment groups.

A total of 320 dogs were included in the field study safety analysis. Abnormal health observations reported in dogs treated with CONVENIA and cefadroxil are summarized in Table 19.

Table 19: Number of Dogs* with Adverse Reactions Reported During the Study with CONVENIA

Adverse Reactions	CONVENIA n = 157	Cefadroxil n = 163
Lethargy	2	7
Anorexia/Decreased Appetite	5	8
Vomiting	6	12
Diarrhea	6	7
Blood in feces	1	2
Dehydration	0	1
Flatulence	1	0
Increased Borborygmi	1	0

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

c. Injection Site Observations:

CONVENIA or injectable placebo was administered by the examining veterinarian subcutaneously at a site free of any pre-existing abnormalities and not near the sites of other injectable treatments. Injections were administered in five anatomical regions: thorax, forelimb, hind limb, dorsal scapula, or lumbar region. The percentage of CONVENIA-treated dogs receiving treatment at each site are as follows: thorax 24%, left and right forelimb 35%, left and right hind limb 13%, dorsal scapula 20%, and lumbar 8%. This included dogs receiving injections on Day 0 and Day 14.

There were no abnormal injection site observations in CONVENIA-treated dogs.

d. Clinical Pathology:

There were no clinically significant differences between mean values for all laboratory tests among CONVENIA and cefadroxil-treated dogs. For individual laboratory values the following findings were noted:

Eight CONVENIA-treated dogs had normal gamma glutamyl transferase (GGT) levels pre-study (normal range: 0 - 10 IU/L) and elevated levels post-study (range 11 - 21 IU/L).

Four CONVENIA-treated dogs had normal alanine aminotransferase (ALT) levels pre-study (normal range: 0 - 120 IU/L) and elevated levels post-study (range 134 - 454 IU/L).

Four CONVENIA-treated dogs had normal ALP levels pre-study (normal range: 21 - 125 IU/L) and elevated ALP levels post-study (range 136 - 144 IU/L).

Seven CONVENIA-treated dogs had normal platelet counts pre-study (normal range: 2-5 x 10^5/mm^3) and decreased platelet counts post-study (range 1.4 to 1.9 x 10^5/mm3). One CONVENIA-treated dog had a pre-study platelet count of 1.9 x 10^5/mm^3, a post-study count of 0.4 x 10^5/mm^3, and giant platelets were observed on the blood smear. In this animal, the red blood cell count was below normal both pre- and post-study but increased slightly from 4.76 to 5.07 x 10^6/mm^3 over the course of the study (normal range 5.5 - 8.5 x 10^6/mm^3). Clinical manifestations of thrombocytopenia were not documented.

e. Microbiology:

CONVENIA is a cephalosporin antibiotic. Like other β-lactam antimicrobials, CONVENIA exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. For *E. coli*, the *in vitro* activity of CONVENIA is comparable to other cephalosporins, but due to the high-affinity protein-binding, the *in vivo* free concentration of cefovecin does not reach the MIC_{90} for *E. coli* (1.0 mcg/mL). CONVENIA is not active against *Pseudomonas* spp. and enterococci.

Identification of bacterial pathogens was made to the species level, based on morphology, Gram stain, growth characteristics, standard individual biochemical testing, and/or commercially available identification test kits. Minimum inhibitory concentration (MIC) testing was conducted in accordance with applicable Clinical and Laboratory Standards Institute (CLSI) standards.

CONVENIA MICs for the pre-treatment bacterial pathogens isolated from enrolled dogs are summarized in Table 20.

Table 20: Activity of CONVENIA Against Pathogens Isolated from Dogs Treated With CONVENIA in Field Studies in the U.S. During 2001-2003

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Skin infections	*Staphylococcus intermedius*	Success	44	Pre-Treatment	0.12	0.25	≤0.06 - 2
		Failure	4	Pre-Treatment			0.12 - 2
	Streptococcus canis (Group G)	Success	16	Pre-Treatment	≤0.06	≤0.06	≤0.06
		Failure	2	Pre-Treatment			≤0.06

6. Conclusions:

CONVENIA administered as a subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight was effective for the treatment of skin infections (superficial secondary pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G). Twenty-two CONVENIA-treated dogs required two injections.

VI. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Michael C. Savides, PhD.
Ricerca, LLC
Concord, OH

3. General Design:

a. Purpose: To determine the toxic effects of CONVENIA when administered once subcutaneously to dogs at an exaggerated dose (180 mg/kg body weight).

b. Test Animals: Twelve healthy Beagle dogs (6M and 6F), approximately seven months of age, were randomly assigned to one of two groups. Six dogs (3/sex) were randomly assigned to the CONVENIA group and six dogs (3/sex) were randomly assigned to the control group.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of injectable CONVENIA

e. Route of administration: dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for the Drug Tolerance Study

Group	Dose mg/kg	Number and Sex of Dogs
1	0 mg/kg (saline)	3 males, 3 females
2	180 mg/kg	3 males, 3 females

g. Test duration: Thirty days

h. Variables measured: Clinical observations, physical exams, injection site evaluations, body weights, hematology, serum chemistry, coagulation tests, plasma drug concentrations, urinalysis, and food consumption were assessed.

4. Results: All dogs survived to termination of the study.

a. Abnormal clinical findings included irritation, scratching/chewing at the injection site and vocalization following administration in four CONVENIA-treated dogs and three control dogs. Edema ventral to the injection site was observed in six CONVENIA-treated dogs and three control dogs during the first 8 hours post-dosing. All edema resolved within 24 hours of dosing. One CONVENIA-treated dog vomited on Day 23 of the study, with no other clinical abnormalities noted.

b. Hematology: There was a trend for the APTT (activated partial thromboplastin time) values to be higher in the CONVENIA-treated group compared to the control group, although all values remained within the reference range used for this study[2].

c. Clinical chemistry evaluations showed higher mean alkaline phosphatase values for the CONVENIA-treated dogs on Days 10 and 30 compared to the control dogs. All values stayed within the normal reference range.

d. Plasma drug concentrations: In both male and female animals, concentrations of CONVENIA were greatest at the initial sampling time (1.5 hours), and remained above the limit of detection (0.05 µg/ml) for the duration of the study. These data indicate that CONVENIA was rapidly absorbed and that there was a prolonged time for elimination from the plasma.

[2] Duncan, J. R., Prasse K. W. Veterinary Laboratory Medicine Clinical Pathology, 2nd edition, 1986.

5. Conclusions: Under the conditions of this study, the dogs remained healthy throughout the 30-day duration. Irritation following injection and transient injection site edema occurred in both the control and CONVENIA-treated dogs. The edema resolved within 24 hours.

B. **Margin of Safety and Injection Site Tolerance of Cefovecin Injectable Solution in Dogs:**

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Elizabeth Evans, DVM
Midwest Research Institute (MRI)
Kansas City, MO

3. General Design:

a. Purpose: To evaluate the safety and injection site toleration of CONVENIA when administered subcutaneously once every 7 days for a total of five injections in dogs.

b. Test Animals: Thirty-two healthy Beagle dogs (16M and 16F), approximately 4 months of age, were randomly assigned to the four dose groups.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for Safety Study

1) Control (saline) every seven days for four consecutive weeks (5 total doses)
2) 12 mg/kg (1.5 X) every seven days for four consecutive weeks (5 total doses)
3) 36 mg/kg (4.5 X) every seven days for four consecutive weeks (5 total doses)
4) 60 mg/kg (7.5 X) every seven days for four consecutive weeks (5 total doses)

g. Test duration: Forty-two days

h. Variables measured: Evaluations included clinical signs, general health observations, physical examinations, body weight, hematology, coagulation tests, serum chemistry, urinalysis, fecal examination, gross pathology and histopathology, injection site evaluations, and plasma blood concentrations.

4. Results: All dogs survived to termination of the study.

a. Clinical observations: There were observations of red and inflamed ears of dogs in all study groups. This occurrence may have been related to husbandry conditions, and resulted in 63 occurrences in the control group, 77 occurrences in the 12 mg/kg (1.5 X) group, 76 occurrences in the 36 mg/kg (4.5 X) group, and 135 occurrences in the 60 mg/kg (7.5 X) group.

Alopecia was reported in several dogs among all groups throughout the study, and was attributed by the study veterinarian to traumatic rubbing.

Other abnormal clinical findings included seven CONVENIA-treated dogs with red scleras at Day 7. Throughout the study there was one case of soft stool in the control group, two cases in the 36 mg/kg group, and one case in the 60 mg/kg group. There was one incidence of vomiting in the control group, two cases in the 12 mg/kg group, three in the 36 mg/kg group, and five cases in the 60 mg/kg group. Additionally, a 60 mg/kg dog with an elevated temperature and panting was noted on Day 27. No other problems were noted in this dog.

b. Hematology: Generally, for all four groups in the study, the prothrombin time (PT) was shorter (6 - 7 seconds) than the reference range used in this study (13.2 - 22 seconds).[3] Although all groups ran low for the given range, the mean prothrombin time in the 60 mg/kg group males was significantly ($p = 0.0010$) longer than that of the control group.

There were statistically significant differences among treatment groups for white blood cell (WBC) counts. There was significant interaction between the treatment and the time period. The mean values for all the treated groups were statistically significantly lower than the control group at the first, third, fourth and fifth time points. (Time 0 = pre-study, Time 1 = Days 6 - 7, Time 2 = Days 12 - 13, Time 3 = Days 19 - 21, Time 4 = Days 26 - 28, and Time 5 = Days 40 - 41 of the study.) The mean WBC counts for the 36 mg/kg group ($p = 0.0324$), the mean neutrophil count for the 12 mg/kg group ($p = 0.0416$) and the 36 mg/kg group ($p = 0.0787$) were significantly lower than the control group at the second time point.

c. Serum Chemistry: There were statistically significant differences amongst the treated groups for bile acid values. The mean bile acid values for the 12 mg/kg group ($p = 0.0899$) and the 60 mg/kg group ($p = 0.0040$) were statistically significantly higher than that of the control group.

The mean BUN value for the 36 mg/kg group was statistically significantly higher ($p = 0.0088$) than that of the control group.

d. Injection site evaluations:

[3] Bonagura, JD. 1995. Kirk's Veterinary Therapy XII: Small Animal Practice. W.B. Saunders Co., Philadelphia.

Whining and discomfort were noted in two 60 mg/kg dogs during or after dosing on Day 7. Swelling following injections usually appeared by one hour post-administration. The number of animals that showed swellings after each injection for each treatment group is represented in the Table 21. Fisher's exact test was used to test the difference between the control and the treated groups for each injection time.

Table 21: Number of Dogs/Group with Injection Site Swelling

	Control	12 mg/kg	36 mg/kg	60 mg/kg
1st injection	1	1	6*	5
2nd injection	4	3	7	8*
3rd injection	4	3	7	7
4th injection	3	3	7	8*
5th injection	2	4	3	7*

* $p = < 0.1$, statistically significant

A statistically significant number of animals in the 60 mg/kg group showed swellings after each injection compared to the control group following the 2nd, 4th, and 5th injection periods. Also, a statistically significant number of animals in 36 mg/kg group showed swellings compared to the control group following the 1st injection. The maximum swelling measured throughout the study was 6 mm X 6 mm (length X width). Histopathology of the injection sites included 1 erosion/ulcer in the epidermis of one control dog, three 12 mg/kg dogs, four 36 mg/kg dogs, and four 60 mg/kg dogs.

e. Pathology: There was one dog in the 60 mg/kg group that exhibited glomerulopathy on histopathology. There were five treated dogs (one-12 mg/kg dog, one-36 mg/kg dog, and three-60 mg/kg dogs) and two control dogs that exhibited mild lamina propria and/or GALT (gastrointestinal associated lymphoid tissue) hemorrhage along the intestinal tract on histopathology. There was a male in the 60 mg/kg group that had minimal peliosis hepatis.

f. Plasma drug concentrations: A less than dose proportional change in total drug exposure was seen as doses increased from 12 mg/kg to 60 mg/kg in dogs. Accordingly, total drug peak and trough concentrations of CONVENIA in plasma were similar in dogs receiving subcutaneous doses of 12 mg/kg, 36 mg/kg, and 60 mg/kg of CONVENIA. Concentrations were similar between male and female dogs.

5. Conclusions: An adequate safety margin was demonstrated for CONVENIA when administered under the conditions of this study throughout the 42-day study duration. Occurrences of injection site swellings increased with increasing doses of CONVENIA and usually appeared within one hour of administration. Mild hepatic and renal lesions were observed in two of the 60 mg/kg group dogs.

VII. HUMAN FOOD SAFETY:

This drug is intended for use in cats and dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

VIII. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to CONVENIA:

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental human exposure. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefovecin, are advised to avoid direct contact of the product with the skin and mucous membranes".

The following items were examined to ensure human user safety: the material safety data sheet (MSDS) for cefovecin and the data submitted in support of this NADA. According to the MSDS for the active ingredient (dated September 13, 2007, Pfizer), the active ingredient may cause allergic skin reaction upon contact. The above Human Warnings should adequately address this concern.

IX. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514.

The data demonstrate that CONVENIA, when used according to the label, is safe and effective for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

The data also demonstrate that CONVENIA, when used according to the label, is safe and effective for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed in the diagnosis of bacterial infections in cats and dogs, treatment of these conditions, and monitoring for possible adverse reactions of the drug.

B. **Exclusivity:**

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

C. **Patent Information:**

U.S. Patent Number	Date of Expiration
6,020,329	July 22, 2011

X. **ATTACHMENTS:**

Facsimile Labeling:
Package insert
Vial
Carton

convenia®

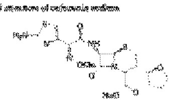
(cefovecin sodium)

Antimicrobial for Subcutaneous Injection in Dogs and Cats Only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Cefovecin sodium is a semi-synthetic broad-spectrum antibacterial agent from the cephalosporin class of chemotherapeutic agents. Cefovecin is the non-proprietary designation for [6R,7R]-7-[[(2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[(2S)-tetrahydro-2-furanyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, monosodium salt.

Figure 1: Chemical structure of cefovecin sodium



Each mL of CONVENIA reconstituted lyophile contains cefovecin sodium equivalent to 80.0 mg cefovecin, methylparaben 1.8 mg (preservative), propylparaben 0.2 mg (preservative), sodium citrate dihydrate 5.8 mg and citric acid monohydrate 0.1 mg, sodium hydroxide or hydrochloric acid as required to adjust pH.

INDICATIONS:

Dogs

CONVENIA is indicated for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

Cats

CONVENIA is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

DOSAGE AND ADMINISTRATION:

Dogs

CONVENIA should be administered as a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) body weight. A second subcutaneous injection of 3.6 mg/lb (8 mg/kg) may be administered if response to therapy is not complete. The decision for a second injection for any individual dog should take into consideration such factors as progress toward clinical resolution, the susceptibility of the causative organisms, and the integrity of the dog's host-defense mechanisms. Therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections. Maximum treatment should not exceed 2 injections.

Cats

CONVENIA should be administered as a single, one-time subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight. After an injection of CONVENIA, therapeutic concentrations are maintained for approximately 7 days for *Pasteurella multocida* infections.

General Dosing Information

A sample of the lesion should be obtained for culture and susceptibility testing prior to beginning antimicrobial therapy. Once results become available, continue with appropriate therapy. If acceptable response to treatment is not observed, or if no improvement is seen within 3 to 4 days, then the diagnosis should be re-evaluated and appropriate alternative therapy considered.

CONVENIA may persist in the body for up to 65 days. The effect of remaining concentrations of cefovecin on any subsequent antimicrobial therapies has not been determined. Fluoroquinolones and aminoglycoside antimicrobials have been reported to be compatible with cephalosporin antimicrobial agents.[1,2,3]

Table 1: Dose Table for CONVENIA at 8 mg/kg Body Weight

Weight of Animal	Volume of CONVENIA (3.6 mg/lb or 0.045 mL/lb)
5 lb	0.23 mL
10 lb	0.45 mL
15 lb	0.67 mL
20 lb	0.90 mL
40 lb	1.8 mL
80 lb	3.6 mL

PREPARATION OF SOLUTION FOR INJECTION: To deliver the appropriate dose, aseptically reconstitute CONVENIA with 10 mL Sterile Water for Injection. Shake and allow vial to sit until all material is visually dissolved. The resulting solution contains cefovecin sodium equivalent to 80 mg/mL cefovecin. CONVENIA is light sensitive. The vial should be stored in the original carton and refrigerated when not in use. Use the entire contents of the vial within 28 days of reconstitution.

CONTRAINDICATIONS: CONVENIA is contraindicated in dogs and cats with known allergy to cefovecin or to β-lactam (penicillins and cephalosporins) group antimicrobials. Anaphylaxis has been reported with the use of this product in foreign market experience. If an allergic reaction or anaphylaxis occurs, CONVENIA should not be administered again and appropriate therapy should be instituted. Anaphylaxis may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, corticosteroids, and airway management, as clinically indicated. Adverse reactions may require prolonged treatment due to the prolonged systemic drug clearance (65 days).

WARNINGS: *Not for use in humans. Keep this and all drugs out of reach of children.* Consult a physician in case of accidental human exposure. For subcutaneous use in dogs and cats only. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefovecin, are advised to avoid direct contact of the product with the skin and mucous membranes.

PRECAUTIONS:

Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

The safe use of CONVENIA in dogs or cats less than 4 months of age (see **Animal Safety**) and in breeding or lactating animals has not been determined. Safety has not been established for IM or IV administration. The long-term effects on injection sites have not been determined. CONVENIA is slowly eliminated from the body, approximately 65 days is needed to eliminate 97% of the administered dose from the body. Animals experiencing an adverse reaction may need to be monitored for this duration.

CONVENIA has been shown in an experimental in vitro system to result in an increase in free concentrations of carprofen, furosemide, doxycycline and ketoconazole. Concurrent use of these or other drugs that have a high degree of protein-binding (e.g. NSAIDs, propofol, cardiac, anticonvulsant, and behavioral medications) may compete with cefovecin binding and cause adverse reactions.

Positive direct Coombs' test results and false positive reactions for glucose in the urine have been reported during treatment with some cephalosporin antimicrobials. Cephalosporin antimicrobials may also cause falsely elevated urine protein determinations. Some antimicrobials, including cephalosporins, can cause lowered albumin values due to interference with certain testing methods.

Occasionally, cephalosporins and NSAIDs have been associated with myelotoxicity, thereby creating a toxic neutropenia[4]. Other hematological reactions seen with cephalosporins include neutropenia, anemia, hypoprothrombinemia, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), platelet dysfunction and transient increases in serum aminotransferases.

ADVERSE REACTIONS:

Dogs

A total of 320 dogs, ranging in age from 8 weeks to 19 years, were included in a field study safety analysis. Adverse reactions reported in dogs treated with CONVENIA and the active control are summarized in Table 2.

Table 2: Number of Dogs* with Adverse Reactions Reported During the Field Study with CONVENIA

Adverse Reaction	CONVENIA (n=157)	Active Control (n=163)
Lethargy	2	7
Anorexia/Decreased Appetite	5	9
Vomiting	8	12
Diarrhea	6	7
Blood in Feces	1	2
Dehydration	0	1
Flatulence	1	0
Increased Borborygmi	1	0

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Mild to moderate elevations in serum gamma glutamyl transferase or serum alanine aminotransferase were noted post-treatment in several of the CONVENIA-treated dogs. No clinical abnormalities were noted with these findings.

One CONVENIA-treated dog in a separate field study experienced diarrhea post-treatment lasting four weeks. The diarrhea resolved.

Cats

A total of 291 cats, ranging in age from 2.4 months (one cat) to 21 years, were included in the field study safety analysis. Adverse reactions reported in cats treated with CONVENIA and the active control are summarized in Table 3.

Table 3: Number of Cats* with Adverse Reactions Reported During the Field Study with CONVENIA.

Adverse Reaction	CONVENIA (n=147)	Active Control (n=144)
Vomiting	10	14
Diarrhea	7	26
Anorexia/Decreased Appetite	6	6
Lethargy	6	6
Hyperactivity	1	1
Inappropriate Urination	1	0

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Four CONVENIA cases had mildly elevated post-study ALT (one case was elevated pre-study). No clinical abnormalities were noted with these findings.

Twenty-four CONVENIA cases had normal pre-study BUN values and elevated post-study BUN values (37 – 39 mg/dL post-study). There were 4 CONVENIA cases with normal pre- and mildly to moderately elevated post-study creatinine values. Two of these cases also had an elevated post-study BUN. No clinical abnormalities were noted with these findings.

One CONVENIA-treated cat in a separate field study experienced diarrhea post-treatment lasting 42 days. The diarrhea resolved.

FOREIGN MARKET EXPERIENCE: The following adverse events were reported voluntarily during post-approval use of the product in dogs and cats in foreign markets: death, hypersalivation, seizures, anaphylaxis, acute pulmonary edema, facial edema, injection site reactions (alopecia, scabs, necrosis, and erythema), hemolytic anemia, salivation, pruritus, lethargy, vomiting, diarrhea, and inappetence.

For a copy of the Material Safety Data Sheet (MSDS) or to report a suspected adverse reaction call Pfizer Animal Health at 1-800-366-5288.

CLINICAL PHARMACOLOGY:

Pharmacokinetics

Cefovecin is rapidly and completely absorbed following subcutaneous administration. Non-linear kinetics is exhibited (plasma concentrations do not increase proportionally with dose). Cefovecin does not undergo hepatic metabolism and the majority of a dose is excreted unchanged in the urine. Elimination also occurs from excretion of unchanged drug in the bile. Cefovecin is a highly protein bound molecule in dog plasma (98.5%) and cat plasma (99.8%) and may compete with other highly protein bound drugs for plasma protein binding sites that could result in transient, higher free drug concentrations of either compound. Pharmacokinetic parameters following subcutaneous dosing at 8 mg/kg in the dog and cat are summarized in Table 4.

Table 4: Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (mean ± standard deviation or range) Following an 8 mg/kg Intravenous or Subcutaneous Dose of Cefovecin in Dogs and Cats.

PARAMETER	MEAN ± SD† or (Range)	
	Dogs	Cats ‡
Terminal plasma elimination half-life, $T_{1/2}$ (h)*δ	133 ± 16	166 ± 18
AUC_{0-inf} (μg·h/mL)*δ	10400 ± 1900 ‡	22700 ± 3450
Time of maximum concentration, T_{max} (h) *ϑ	6.2 (0.5-12.0)	2.0 (0.5-8.0)
Maximum concentration, C_{max} (μg/mL) *δ	121 ± 51	141 ± 12
Vd_{ss} (L/kg) **δ	0.122 ± 0.011	0.090 ± 0.010
Cl_{total} (mL/h/kg)**ϑ	0.76 ± 0.13 ϑ	0.350 ± 0.40

† SD = standard deviation

‡ = a phase effect was observed; only data for the first phase are provided (n=6); all other data provided are derived from 12 animals

* = SC

** = IV

δ = arithmetic mean

ϑ = harmonic mean

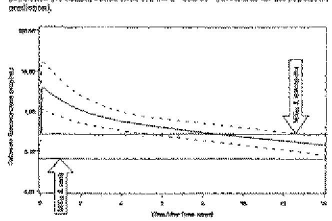
θ = geometric mean

Population Pharmacokinetics

Dogs

Cefovecin plasma concentrations in the dog have been characterized by the use of population pharmacokinetic (PPK) data. Plasma cefovecin concentration data were pooled from seven laboratory pharmacokinetic studies, each involving young, normal healthy Beagle dogs. The final dataset contained 597 concentration records from 59 dogs. The simulations from the model provide the mean population estimate and the 5th and 95th percentile of the population estimates of total and free cefovecin concentrations over time. Figure 2 shows the predicted free plasma concentrations following administration of 8 mg/kg body weight to dogs. Based upon these predicted concentrations, 95% of the canine population will have active (free) drug concentrations > the MIC_{90} of *S. canis* (0.06 μg/mL) for approximately 14 days and free concentrations > the MIC_{90} for *S. intermedius* (0.25 μg/mL) for approximately 7 days following a single 8 mg/kg subcutaneous injection of cefovecin. (See **MICROBIOLOGY**.)

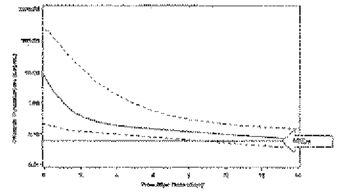
Figure 2: Population Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Dogs (solid line is population prediction, dotted lines are the 5th and 95th percentiles for the population prediction).



Cats

Cefovecin plasma concentrations in the cat have been characterized by the use of PPK data. Plasma cefovecin concentration data were pooled from four laboratory pharmacokinetic studies. The final dataset contained 298 concentration records from 22 cats. The simulations from the model provide the mean population estimate, as well as the 5th and 95th percentile of the population estimates of total and free cefovecin concentrations over time. Figure 3 displays the predicted free plasma concentrations following administration of 8 mg/kg body weight to cats. Based upon these predicted concentrations, 95% of the feline population will have active (free) drug concentrations > the MIC_{90} of *Pasteurella multocida* (0.06 μg/mL) for approximately 7 days when administered a single 8 mg/kg subcutaneous injection of cefovecin. (See **MICROBIOLOGY**.)

Figure 3: Population Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Cats (solid line is population prediction, dotted lines are the 5th and 95th percentiles for the population prediction).



MICROBIOLOGY: CONVENIA is a cephalosporin antibiotic. Like other β-lactam antimicrobials, CONVENIA exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. For *E. coli*, the in vitro activity of CONVENIA is comparable to other cephalosporins, but due to the high-affinity protein-binding, the in vivo free concentration of cefovecin does not reach the MIC_{90} for *E. coli* (1.0 μg/mL). CONVENIA is not active against *Pseudomonas* spp. or enterococci.

Dogs

The minimum inhibitory concentration (MIC) values for cefovecin against label-claim pathogens isolated from skin infections in dogs enrolled in a 2001-2003 field effectiveness study are presented in Table 5. All MICs were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) standards.

Table 5. Activity of CONVENIA Against Pathogens Isolated from Dogs Treated With CONVENIA in Field Studies in the U.S. During 2001-2003.

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC Range (μg/mL)
Skin infections	*Staphylococcus intermedius*	Success	96	Pre-Treatment	0.12	0.25	≤ 0.06 - 2
		Failure	4	Pre-Treatment			0.12 - 2
	Streptococcus canis (Group G)	Success	96	Pre-Treatment	≤ 0.06	≤ 0.06	≤ 0.06
		Failure	2	Pre-Treatment			≤ 0.06

Cats

The MIC values for cefovecin against *Pasteurella multocida* isolated from skin infections (wounds and abscesses) in cats enrolled in a 2001-2003 field effectiveness study are presented in Table 6. All MICs were determined in accordance with the CLSI standards.

Table 6. Activity of CONVENIA Against Pathogens Isolated from Cats Treated With CONVENIA in Field Studies in the U.S. During 2001-2003.

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} μg/mL	MIC_{90} μg/mL	MIC Range μg/mL
Skin infections	*Pasteurella multocida*	Success	97	Pre-Treatment	≤ 0.06	≤ 0.06	≤ 0.06-0.12
		Failure	1	Pre-Treatment			≤ 0.06

EFFECTIVENESS:

Dogs

In a double-masked, 1:1 randomized canine field study conducted in the United States, the effectiveness of CONVENIA was compared to a cephalosporin active control. In this study, 320 dogs with superficial secondary pyoderma, abscesses, or infected wounds were treated with either a single injection of CONVENIA (n = 157) at 3.6 mg/lb (8 mg/kg) body weight or with an oral active control antibiotic (n = 163), administered twice daily for 14 days. In this study, dogs could receive a second course of therapy 14 days after the initial treatment. Of the 320 enrolled dogs, 22 of 157 dogs received two treatments of CONVENIA and 35 of 163 dogs received two courses of treatment with the active control. In the study, 118 of the 157 enrolled cases were available for effectiveness for CONVENIA, and 117 of the 163 enrolled cases were available for effectiveness of the active control antibiotic. CONVENIA was non-inferior to the active control. Table 7 summarizes the clinical success rates obtained 28 days after the initiation of the final course of therapy.

Table 7: Clinical Outcome Rates by Treatment Group 28 Days after the Initiation of the Final Course of Therapy.

Type of Infection	Dogs	
	CONVENIA (n=118)	Active Control (n=117)
Skin (secondary superficial pyoderma, abscesses, and infected wounds)	109 (92.4%)	108 (92.3%)

CONVENIA was administered concomitantly with other commonly used veterinary products such as heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, routine immunizations, antihistamines, thyroid hormone supplementation, and non-steroidal anti-inflammatory drugs during the field study.

Cats

In a double-masked, 1:1 randomized cat field study conducted in the United States, the effectiveness of CONVENIA was compared to an active control. In this study, 291 cats with infected wounds or abscesses were treated with either a single injection of CONVENIA (n = 147) at 3.6 mg/lb (8 mg/kg) body weight or with an oral active control antibiotic (n = 144), administered once daily for 14 days. CONVENIA was non-inferior to the active control. The clinical success rates were obtained 28 days after the initiation of therapy and are presented in Table 8.

Table 8: Clinical Outcome Rates by Treatment Group 28 Days after the Initiation of Therapy.

Type of Infection	Cats	
	CONVENIA (n=83)	Active Control (n=85)
Skin (wounds and abscesses)	80 (96.4%)	80 (94.1%)

CONVENIA was used concomitantly with other commonly used veterinary products such as heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, and vaccines during the field study.

ANIMAL SAFETY:

Dogs

CONVENIA administered to healthy four month old dogs at doses of 12 mg/kg (1.5 X), 36 mg/kg (4.5 X), and 60 mg/kg (7.5 X) every seven days by demonstrated subcutaneous injections was well-tolerated for a total of 5 doses. Vomiting and diarrhea were seen in all treatment groups, with the incidence of vomiting and the incidence and duration of diarrhea increasing in a dose-related manner. Injection site irritation and transient edema occurred with increasing frequency in a dose-related manner and with repeat injections. Two injection site reactions included a necrosis over the shoulder and swelling lasting > 20 days. Dogs dosed at 36 mg/kg had a significant (p < 0.0009) increase in BUN (all means remained within the normal range) compared to the controls. One dog dosed at 60 mg/kg exhibited a glomerulopathy on histopathology, and one dog in this same group had minimal tubular hyperplasia.

As an exaggerated dose of 180 mg/kg (22.5X) in dogs, CONVENIA caused some injection site irritation, vocalization and edema. Edema resolved within 6-24 hours.

Cats

CONVENIA administered to healthy four month old cats at doses of 12 mg/kg (1.5 X), 36 mg/kg (4.5 X), and 60 mg/kg (7.5 X) every seven days by demonstrated subcutaneous injections was well tolerated for a total of 5 doses. Vomiting and diarrhea were observed in cats, with the incidence of vomiting, and the incidence and duration of diarrhea increasing in a dose-related manner. The mean albumin values for all the CONVENIA-treated cats were significantly lower (p < 0.05) than the control values (all means remained within the normal range) for all time periods. The mean alkaline phosphatase values in the 60 mg/kg group were significantly higher (p < 0.0201) than the control values for all time periods. Injection site irritation and transient edema occurred with increasing frequency in a dose-related manner and with repeat injections. One cat in the 12 mg/kg group had a mild renal tubular and interstitial fibrosis, and one cat in the 12 mg/kg group had mild glomerulosclerosis on histopathology.

As an exaggerated dose of 180 mg/kg (22.5X), CONVENIA was associated with injection site irritation, vocalization and edema. Edema resolved within 6-24 hours. On Day 10, cats had lower mean white blood cell counts compared to the controls. One cat had a small amount of bilirubinuria on Day 10.

STORAGE INFORMATION:

Store the powder and the reconstituted product in the original carton, refrigerated at 2° to 8° C (36° to 46° F). **Use the entire contents of the vial within 28 days of reconstitution.** PROTECT FROM LIGHT. After each use it is important to return the unused portion back to the refrigerator in the original carton. As with other cephalosporins, the color of the solution may vary from clear to amber at reconstitution and may darken over time. If stored as recommended, solution color does not adversely affect potency.

HOW SUPPLIED:

CONVENIA is available as a 10 mL multi-use vial containing 800 milligrams of cefovecin as a lyophilized cake.

REFERENCES:

[1]Pitkin SR, Mossberg PC, and Eliopoulos GM. 2005. Antimicrobial combinations, pp 365-440. In V. Lorian (ed.) Antibiotics in Laboratory Medicine, 5th ed., Lippincott, Williams, and Wilkins, Philadelphia, PA.

[2]Park GM, Choi MK, and Jung IS. Synergic activity of cephalosporins plus fluoroquinolones against *Pseudomonas aeruginosa* with resistance to one or both drugs. *Journal of Antimicrobial Chemotherapy* (2002) 50, 1045-1049.

[3]Meyer I and Nagy E. Investigation of the synergic effects of aminoglycoside-fluoroquinolone and third-generation cephalosporin combinations against clinical isolates of *Pseudomonas* spp. *Journal of Antimicrobial Chemotherapy* (1999) 43, 655-657.

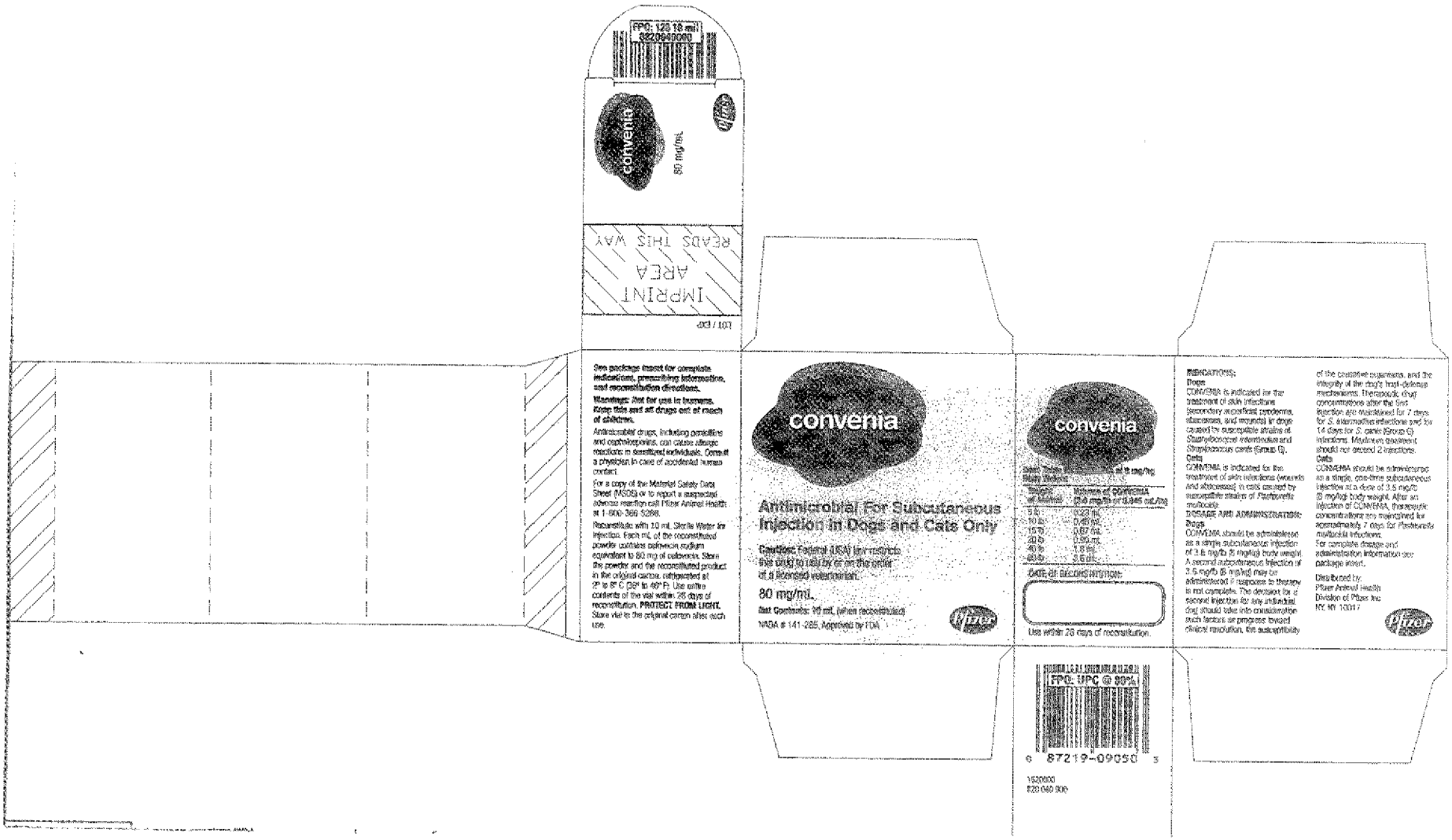
[4]Birchard SJ and Sherding RG. Saunders Manual of Small Animal Practice, 2nd edition. W.B. Saunders Co. 2000: p. 166.

NADA# 141-285, Approved by FDA

Distributed by
Pfizer Animal Health
Div. of Pfizer Inc
NY, NY 10017

January 2009
[illegible]
[illegible]

convenia
Antimicrobial For Subcutaneous Injection in Dogs and Cats Only
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
20 mg/mL
Net Contents: 50 mL (when reconstituted)
NADA # 141-285, Approved by FDA
Pfizer Animal Health
Division of Pfizer Inc, NY, NY 10017



Veterinary Medicine Research and Development
Pfizer Inc
7000 Portage Road; RIC-190-43
Kalamazoo, MI 49001-0102
Tel 269 833 3278 Tel 800 253 8600 ext 33278
Fax 860 715 7951
Email dawn.m.cleaver@pfizer.com

EXHIBIT E

Pfizer Animal Health

Dawn M. Cleaver, D.V.M.
Associate Director
Regulatory Affairs

Dr. Melanie Berson, Director
Division of Therapeutic Drugs for Non-Food Animals (HFV-110)
C/o Document Control Unit (HFV-199)
FDA/Center for Veterinary Medicine
7500 Standish Place
Rockville, Maryland 20855

RE:
- **NADA 141-285; CONVENIA® (cefovecin sodium) for Subcutaneous Injection in Dogs and Cats**
- **Administrative New Animal Drug Application (NADA)**

Dear Dr. Berson:

Under the provisions of Title 21 CFR 514.1, Pfizer Animal Health (PAH) requests approval of this Administrative New Animal Drug Application (NADA) to provide for the use of CONVENIA® (*cefovecin sodium*) injectable for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of Staphylococcus intermedius and Streptococcus canis (Group G) and the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of Pasteurella multocida.

All data required to support the approval of this NADA were submitted and reviewed as phased components for each technical section under INAD 10-612 and 10-613. All requirements to meet the standards for the approval of this NADA have been fulfilled as indicated by the "Technical Section Complete" letters included in each phased technical section of the attached NADA. The Animal Drug User Fee for this application has been provided to FDA under the Payment Identification Number AD1000179-953877 (a copy of the cover sheet is included).

On March 12, 2008, Pfizer requested a revision to the FOI to remove the statement on page 13 of the FOI document (I-010612-Q-0237-OT and I-010613-Q-232-OT) concerning 23 CONVENIA cases with elevated post-treatment bilirubin levels. This statement was previously determined to be an error (e-mails of February 21, 2008) but inadvertently retained in the FOI document. Dr. Michele Sharkey confirmed the revisions would be made during the NADA process in an e-mail dated March 12, 2008. A copy of this e-mail has been included in Section 11 of this aNADA.

NADA 141-285
March 13, 2008

We believe that this application is complete for the purpose of approval. Your Division's (HFV-110) guidance for the content of this application and phased review for INADs 10-612 and 10-613 has been greatly appreciated. Please do not hesitate to contact me if there are questions regarding this application.

Kind regards,

for

Dawn M. Cleaver

DEPARTMENT OF HEALTH & HUMAN SERVICES

RECEIVED
MAR 26 2008
WW Animal Health
Regulatory Affairs

Food and Drug Administration
Rockville MD 20857

NADA 141-285

March 18, 2008

Pfizer Inc
Attn: Dawn M. Cleaver
Associate Director Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

EXHIBIT F

Dear Dr. Cleaver:

We acknowledge receipt of your submission dated March 13, 2008, which pertains to the establishment of a New Animal Drug Application for the use of cefovecin sodium in cats and dogs.

Your submission has been assigned **NADA number 141-285**. Please refer to this number when submitting any future correspondence pertaining to this application.

The application is being forwarded to the appropriate division for review.

This is not an approval letter.

Sincerely,

Daniel Williams
Technical Information Specialist
Center for Veterinary Medicine
HFV-199

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

N-141285-A-0000-OT

RECEIVED

MAY 0 9 2008

WW Animal Health
Regulatory Affairs

APR 2 5 2008

Pfizer, Inc.
Attention: Dawn M. Cleaver, D.V.M.
Associate Director
Regulatory Affairs
7000 Portage Road; RIC-190-43
Kalamazoo, MI 49001-0102

EXHIBIT G

Re: Request for original approval of CONVENIA

Dear Dr. Cleaver:

We approve your original new animal drug application (NADA) for CONVENIA dated March 13, 2008, under section 512(c)(1) of the Federal Food, Drug, and Cosmetic Act (the act). CONVENIA (cefovecin sodium) Injectable Solution is approved for the treatment of skin infections (wounds and abscesses) caused by susceptible strains of *Pasteurella multocida* in cats; and the treatment of skin infections (secondary superficial pyoderma, abscesses and wounds) caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G) in dogs. The expiration dating for this new animal drug is 24 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this approval according to 21 CFR 514.8. Any change to the conditions of the approval may require the submission of a supplemental application.

CONVENIA, as approved in this letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of this letter. Your new animal drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the act because no active ingredient of the new animal drug has previously been approved.

Your final printed labeling must be identical to the approved labeling submitted March 13, 2008 (N-141285-A-0000-OT). Please submit in triplicate three paper copies (a total of nine copies) of each component of the final printed labeling before distributing and marketing your new animal drug. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

Under good manufacturing practice (cGMP) regulations (21 CFR 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval

inspection, you should contact FDA after you complete manufacturing validation and before you ship the drug product. A product that does not conform to cGMP is adulterated under section 501(a)(1)(B) of the act.

If you submit correspondence relating to this approval, your correspondence should reference the date and principal submission identifier(s) found at the top of this letter. If you have any questions, please contact Dr. Melanie R. Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 240-276-8337.

Sincerely,

Bernadette Dunham, DVM, PhD

Bernadette Dunham, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary